A Review
on
Triple-Negative Breast Cancer and its Potential Treatment

By

Jannatul Ferdous Niasa
18146073

A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing 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 which 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.

Student's Full Name & Signature:

Jannatul Ferdous Niasa
18146073

Approval

The project titled "A Review on Triple-Negative Breast Cancer and its Potential Treatment" submitted by Jannatul Ferdous Niasa (18146073) of Summer, 2021 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on May 2022.

Examining Committee:

Supervisor:

_____

(Member)

Namara Mariam Chowdhury
Lecturer, School of Pharmacy
Brac University

Program Coordinator:

_____

(Member)

Namara Mariam Chowdhury
Lecturer, School of Pharmacy
Brac University

Deputy Chair:

_____

(Member)

Hasina Yasmin, PhD
Professor, School of Pharmacy
Brac University

Dean:

_____ Eva Rahman Kabir, PhD
Professor and Dean, School of Pharmacy
Brac University

Ethics Statement

This study does not involve any human or animal trial.

Abstract

Triple-negative breast cancer is defined as breast cancer that lacks estrogen, progesterone, and the human epidermal growth factor receptor 2. (TNBC). This malignancy accounts for 15–20 percent of all breast cancers and is of particular interest for study because of its clinically problematic low treatment response and highly invasive features. Due to the lack of particular treatment options for TNBC, conventional therapy such as adjuvant and neoadjuvant therapy, surgery, immunotherapy, and radiation therapy are frequently used. The focus of this review is to provide information related to TNBC diagnosis and survival rate, biomarkers, different signaling pathways as well as current and investigation therapies, prognosis, and some advanced research about drugs and therapies. Researchers working in the area may find the data offered in this publication useful in obtaining general and specific information to increase their understanding of TNBC and provide appropriate disease management in the future.

Keywords: TNBC; HER-2 receptors, anti-cancer therapeutics; signaling pathways.

Dedication

Dedicated to my beloved spouse, my parents, and my youngest brother. Without their support and inspiration, this special journey of the thesis would not be easy.

Acknowledgment

First and foremost, I thank my Almighty Allah, all gratitude to Allah for bestowing upon me enormous patience and strength throughout the whole journey. It was a crucial time for all of

us during this pandemic as there are ups and downs in everyone's life. Thanks to Allah for helping me to cope with this situation.

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List of Acronyms

TNBC	Triple-negative breast cancer
BRCA1	Breast Cancer gene 1
BRCA2	Breast Cancer gene 2
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
Wnt	Wingless-related integration site
DBD	DNA-binding domain
ERE	Estrogen response elements
CDK	Cyclin-dependent kinase
MAPK	Mitogen-activated protein kinase
PI3K	Phosphoinositide 3-kinases
GSK	Glycogen Synthase Kinase
TCF	T-cell factor
LEF	Lymphoid improvement factor
CCND1	Cyclin D1
DKK1	Dickkopf-related protein 1
BRK	Breast Tumor Kinase
S6K	Ribosomal protein S6 kinase
DCIS	Ductal Carcinoma in situ

LCIS	Lobular Carcinoma in situ
IDC	Ductal carcinoma, infiltrating or invasive
ILC	Lobular Carcinoma with Infiltrating Carcinoma
VEGF	Vascular endothelial growth factor
NTRK	Neurotrophic tyrosine receptor kinase
PCR	Polymerase chain reaction

Chapter 1 Introduction

1.1 What is Cancer?

Cancer is a disease in which abnormal cells proliferate uncontrollably in any part of the body. These cells can affect healthy human tissues. The name of the tissue from which the rare cells originated is used to identify many malignancies, as well as the rare cells that make up cancer tissue (e.g., breast cancer, lung cancer, and colorectal cancer). Cells do not die when they are wounded or unrepaired. Cancer cells divide and develop at an uncontrollable rate, resulting in a tumor. Cancer cells frequently break apart from their initial cell mass and travel through the bloodstream. They penetrate the circulation and lymphatic systems before settling in other organs, where they might restart the uncontrolled growth cycle. This process is called metastasis. (Becker, L. 2013).

There are over 100 types of cancer. Forms of cancer are sometimes named for the organs or tissues wherever the cancer type is. for instance, carcinoma starts within the respiratory organ, and brain cancer starts within the brain. Cancer is once abnormal cells divide in associated uncontrolled means. Some cancers might eventually unfold into different tissues.

RISK FACTORS:

The majority of individuals are unaware that cancer can be avoided in many circumstances. The first step in cancer prevention is to understand the causes of cancer and its risk factors.

Radiation Exposure: The most common source of radiation exposure is the sun. Radon gas, which can be present in the soil and collect in your home, is another potential cause of environmental exposure. Anyone could also become exposed as a result of medical imaging or therapy.

Infections: Infections can raise our cancer risk in a variety of ways. Some viral infections directly cause cancerous changes in the DNA. Other infections can result in long-term inflammation, which raises our chances of getting cancer. Other disorders, such as HIV, weaken the immune system, making it incapable of defending the body against cancer growth.

The human papillomavirus increases the risk of cervical, anal, vulvar, and vaginal malignancies

(HPV). According to studies, HPV appears to play a role in a variety of head and neck cancers, and researchers are still investigating its impact on other malignancies. Girls and boys should get the HPV vaccine when they are 11 or 12 years old.

Age: While most cancers can strike all people at any age, the common age of most cancer analyses is sixty-five to seventy-four years old, relying on the type. We had been uncovered to greater cancer agents and inflammatory strategies over time, and slow-developing malignancies have had greater time to come to be symptomatic. Our body's capacity to hit upon and kill malignant and pre-cancerous cells additionally deteriorates. However, a few cancers, together with bone most cancers and a few forms of leukemia, are greater, and not unusual place in children.

Genetics: All malignancies are due to mutations withinside the genes, however, withinside the considerable majority of cases, those mutations are obtained and now no longer surpassed right down to our offspring. Although one has "good" DNA, a mutation in a single molecular can motivate it to proliferate out of control. Oncogenes and inactivated tumor suppressor genes are not unusual to place reasons underlying most cancer risks.

However, most cancers are due to an own circle of relatives most cancer syndrome may be inherited in 5% to 10% of instances. Taking greater care if one has an own circle of relatives with records of most cancers, consisting of breast cancers, is critical. For a few hereditary malignancies, genetic assessments are available. It's critical to recollect that simply due to the fact one has an own circle of relative’s records of most cancers would not suggest he/she can be able to get it. It depends on the time earlier than they broaden it (a genetic predisposition).

Many of the primary cancer risk factors are within our control. For people who are aware of certain predispositions, this can be very empowering.

Tobacco: Smoking tobacco not only harms the lungs but also raises the risk of numerous cancers. In reality, smoking is responsible for 30% of all cancer fatalities in the United States, and it is also responsible for 80% of lung cancer deaths. Quitting smoking immediately lowers our cancer risk factors.

Alcohol:

Alcohol is an irritant that damages the cells and encourages the formation of most cancersinflicting materials withinside the colon. The American Cancer Society recommends restricting alcohol intake to 1 drink in line with day for ladies and beverages in line with day for guys to reduce most cancer risks.

Physical Activity Deficit:

Exercising for at least half-hour 5 days every week lowers most cancers hazard significantly. We do not need to run marathons to be successful. Even mild activity, inclusive of operating withinside the lawn some days every week, has been proven to lessen the prevalence of lung cancers and different varieties of most cancers.

Obesity:

Obesity is one of the maximum not unusual place reasons for most cancers. Breast most cancers, colon and rectal most cancers, endometrial most cancers, esophageal most cancers, pancreatic most cancers, and kidney most cancers are only some of the sicknesses it can cause. Excess fat cells create extra estrogen and insulin, chemical compounds that inspire most cancer growth. We can decrease our dangers with the aid of using attaining or preserving a wholesome frame weight.

Diet:

The best manner to lessen most cancers threat is to devour a plant-primarily based eating regimen that consists of vegetables, entire fruit, entire grains, and protein from peas and beans. Limit one's consumption of processed meats, pink meat, sugar-sweetened beverages, and delicate carbohydrates.

Exposure to the Sun:

Excessive exposure to UV radiation from the sun can result in pores and skin cancers. Sunburn, like tan, is the result of sun harm to the pores and skin.

Many occurrences of pores and skin cancers may be averted with a touch of forethought. Wearing sunscreen is beneficial, however, one ought to additionally exercise secure solar publicity. Avoid direct daylight between the hours of 10 a.m. and a pair of p.m., take a seat down under an umbrella, put on shielding clothing, and keep in mind our sunglasses. Melanoma is a kind of pores and skin most cancers that usually influences the eyes. (Fayed, 2021)

Figure 1: Some risk factors for cancers

adapted from https://www.istockphoto.com/photos/cancer-risk-factors

1.2 Classification of cancer

Hundreds of billions of cells make up our body. We can most effectively see the cells below a microscope in view that they may be so little. Our frame's tissues and organs are made of cells that might be grouped. They have loads in common. However, because those frame organs carry out pretty numerous functions, they vary in diverse respects. Nerves and muscles, for example, carry out diverse functions, subsequently, their cells have special architectures. There are over two hundred special sorts of most cancers, and we might also additionally categorize them primarily based totally on wherein they start withinside the frame, which includes breast cancers or lung cancers. We also can categorize cancers primarily based totally on the kind of cell that they start in. There are five major categories. Those are discussed below:

I. **Carcinoma:** It starts in the skin or in the tissues that line or cover internal organs. The epithelial layer of cells that forms the lining of exterior sections of the body or the interior linings of organs within the body gives rise to this type of cancer. Carcinomas, or cancers of epithelial tissue, account for 80 to 90% of all cancer cases because epithelial tissues are located throughout the body, from the skin to the covering and lining of organs and internal passageways like the gastrointestinal tract. Carcinomas most commonly affect secreting organs or glands, such as the breast, lungs, bladder, colon, and prostate. There are some subtypes which include Adenocarcinoma, basal cell carcinoma, squamous cell carcinoma, and transitional cell carcinoma.

II. **Sarcoma:** Sarcoma is one kind of cancer that starts in the connective or supporting tissues of the body. Tumors of the connective and supporting tissues, such as muscles, bones, cartilage, and fat, are the source of these cancers. Osteosarcoma is a type of sarcoma that affects the bones. The young are the ones who are most affected. Sarcomas take on the appearance of the tissue in which they develop.

III. **Leukemia:** It is a form of cancer that influences white blood cells. It starts withinside the bone marrow and different organs that produce blood cells. This is a set of cancers that fall below the class of blood cancers. These malignancies assault the bone marrow, that's answerable for the era of blood cells. When the bone marrow will become malignant, it produces an overabundance of immature white blood cells that fail to carry out their functions, leaving the affected person at risk of infection.

IV. **Lymphoma:** Lymphocytic malignancies are tumors of the lymphatic system. Unlike leukemias, which are "liquid tumors" that affect the blood, lymphomas are "strong malignancies." These can affect lymph nodes in precise places along with the stomach, brain, and intestines. Extranodal lymphomas are a sort of lymphoma that takes place outdoor of the lymph nodes.

V. **Myeloma:** These are made in the bone marrow's plasma cells. In response to infections, plasma cells can produce a variety of antibodies. Myeloma is a form of cancer that affects the blood.

1.3 What is breast cancer?

Breast cancer is the most prevalent cancer in women, accounting for almost one-tenth of all new diagnoses each year. It is the second leading cause of cancer death in women worldwide. The milk-producing glands of the breast are found in the front of the chest wall. They're maintained in place by ligaments in the pectoralis major muscle that attach the breast to the chest wall. The breast is made up of 15 to 20 lobes that can be organized in a circular pattern. The fats that coat the lobes determine the length and shape of the breasts. Each lobe is made up of lobules, which contain milk-producing glands that respond to hormone stimulation. Breast cancer grows unnoticed at all times. Routine screenings are how the majority of people learn about their disease. Others may experience an unnoticed breast lump, a change in the form or size of their breasts, or nipple discharge. A physical examination, imaging, particularly mammography, and tissue biopsy are all required to identify breast cancer. The chances of survival increase when cancer is detected early. The tumor tends to spread lymphatic and hematologically, which might lead to distant metastasis and a poor prognosis. In this approach, the value of breast cancer screening applications is defined and reinforced. Breast cancer is a disease in which the cells of the breast get uncontrollably large. There are several forms of breast cancer. Which cells within the breast evolve into malignant cells determines the type of breast cancer. Breast cancer can begin in several different locations within the breast. Lobules, ducts, and connective tissue are the three most significant components of a breast. Lobules are the glands that produce milk. The milk travels from the breast to the nipple viaducts, which are tubes running from the breast to the nipple Connective tissue, which is made up of fibrous and fatty tissue, holds everything together. Breast cancers typically develop within the ducts or lobules of the breast. Breast cancers can spread to other parts of the body via blood and lymph arteries. Breast cancer is said to have metastasized when it spreads to different parts of the body. (Simon, A., & Robb, K.2021).

Several inherited mutant genes that may increase the risk of breast cancer have been identified. The most well-known are breast cancer genes 1 (BRCA1) and 2 (BRCA2), both of which significantly enhance the risk of breast and ovarian cancer.

The majority of people imagine a lump inside the breast when they think of breast cancer detection. This is a possible warning signal; however, it isn't the most effective. It's also possible that it won't be the first to sprout.

On a cellular level, there are numerous parallels between everyday improvement and the progression of most malignancies. Throughout human development, complex signaling networks that allow cells to communicate with one another and with their surroundings are meticulously maintained. It is not surprising that many of the same signaling pathways are downregulated or impaired in most cancer cells and CSCs. Cancer is generally caused by genetic and epigenetic changes that allow cells to bypass the systems that prevent them from properly reproducing, surviving, or migrating. Many of these modifications are regulated by signaling networks that regulate cell proliferation, division, death, differentiation, and motility. As a result, proto-oncogene activating mutations may enhance signaling pathway hyperactivation, whereas tumor suppressor inactivation eliminates key signaling bad regulators. The primary signaling pathways that regulate normal mammary gland growth and breast cancer stem cell activity, including estrogen receptor (ER) signaling, HER2 signaling, and canonical Wnt signaling, will be reviewed below:

ER signaling and breast cancer that is ER-positive:

Estrogen receptors are made up of membrane estrogen receptors (specifically G proteincoupled receptors) and nuclear estrogen receptors (ER, ER) (ERs). Both ER and ER are transcriptional elements that can activate or inhibit the expression of target genes in response to ligand binding. ER (coded via way of means of ESR1) and ER (coded via way of means of ESR2) have structural similarities that serve their number one sports at the same time as preserving receptor-particular sign transduction through wonderful components. Both ER and ER own six practical domain names which can be much like various ranges and might shape heterodimers. The DNA-binding domain (DBD), which mediates the interaction of ER dimers with estrogen response elements (EREs) of target genes, has the highest identification rate of 96%. In addition to the ERE-structured method, ERs can change transcription without the participation of EREs. Many co-activators and co-repressors, including BRCA1, play significant roles in the ER-mediated transcription law mechanism. BRCA1 operates as a tumor suppressor in part by inhibiting ER signaling. The complexity of ER-mediated signaling indicates that it has a couple of physiologic and pathological functions. ER performs an enormous function withinside the improvement of breast cancers, with a superb expression of this form of hormone receptor visible in around 75% of breast cancers. Many elements affect the activity of ER in breast most cancers biology, and it's far worried in several times of crosstalk. The interplay of ER with cyclin D1 is one of the best-studied methods via way of means by which ER stimulates the improvement of breast carcinoma cells. In many cancer cells, cyclin D1 is a key activator of

CDKs four and 6, which coordinate the transition of the cell cycle from the G1 to the S phase. The synergy between the ER and cyclin D1 feedback loops may also help to explain the mechanism of antiestrogen treatment resistance and provide a foundation for the use of specific CDK4/6 inhibitors in combination with a hormonal treatment in ER + patients.

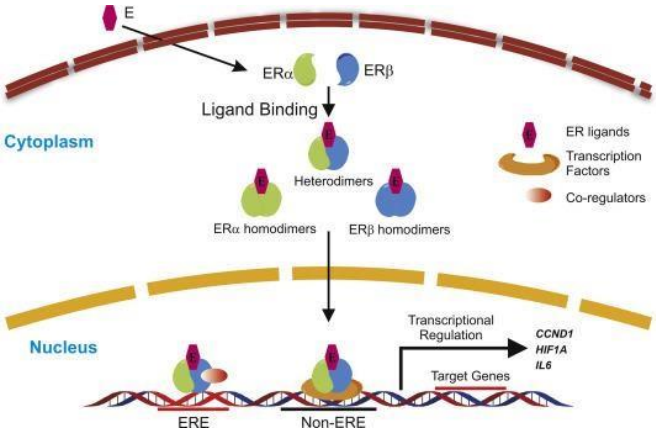

Figure 2: Signaling pathway of ER (Feng, Y. et al., 2018)

HER2 signaling breast cancer that is HER2-Positive: Human epidermal growth factor receptors (EGFRs, or HERs) 1–4 are tyrosine kinase receptors found in both normal and malignant tissues. One of the EGFRs is the human epidermal growth factor receptor-2 (HER2/NEU, c-ERBB2). HER2 is a tyrosine kinase receptor with an extracellular ligandbinding domain, a transmembrane domain, and an intracellular domain, like the others. Because of its constitutively active state, HER2 is an attractive component for forming dimers with other molecules, allowing it to influence a wide range of cell functions through several pathways. Ligand binding and dimerization promote phosphorylation of tyrosine residues in the intracellular domain of HER2, which activates several downstream signal transduction pathways, including the mitogen-activated protein kinase (MAPK) and phosphatidylinositol four,5-bisphosphate 3-kinase (PI3K). Those signaling pathways are intimately linked to breast carcinogenesis. Breast cancer cells that explicit HER2 have a better threat of spreading. Progesterone and progesterone-triggered paracrine alerts are ideas to pressure migration in early number one tumor cells, activating mammary stem cells withinside the process. This expected impact is in step with the capabilities of HER2-inspired stem cells which have been seen. As a result, HER2 trying out is used to pick out sufferers who're applicants for an in all likelihood resistant and luxurious remedy. HER2 molecular evaluation has emerged as a

critical thing in the diagnostic breast most cancers affected person work-up with the aim of extended remedy specificity.

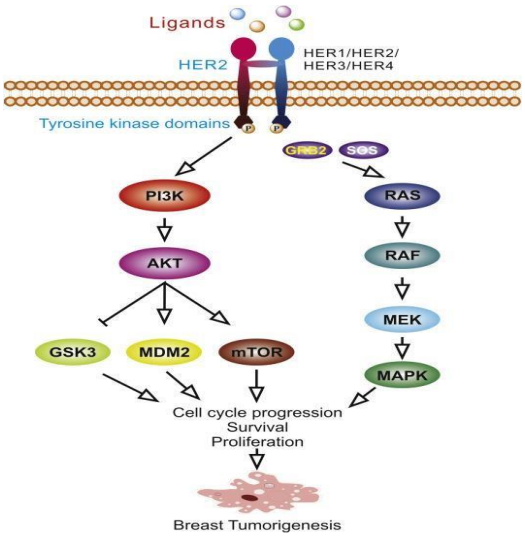

Figure 3: Signaling pathway of HER2 (Feng, Y. et al., 2018)

Canonical Wnt/β-catenin signaling:

Wnt proteins are a family of secreted, glycosylated proteins that are involved in a variety of developmental processes, including embryonic induction, cell polarity creation, and cell fate specification, as well as individual tissue homeostasis. The canonical Wnt/-catenin signaling is triggered by the binding of secreted Wnt proteins to each co-receptor, which may be palmitoylated by Porcupine. Frizzled proteins are LRP5/6 (low-density lipoprotein receptorassociated proteins five and six). Wnt-receptor interaction recruits Axin and Dishelved proteins to the cell membrane and suppresses glycogen synthase kinase (GSK)-three, a negative regulator of the Wnt pathway that leads -catenin to proteasomal degradation via phosphorylation. Catenin accumulates in the cytoplasm and then translocates into the nucleus, where it serves as a co-transcriptional activator with CREB binding protein (CBP) and T-cell factor/lymphoid improvement factor (TCF/LEF) transcription factors, controlling oncogenes such as MYC and CCND1. Wnt signaling is probably constitutively energetic in breast most cancers through an autocrine mechanism. While Wnt signaling mutations are unusual in breast most cancers, it's been found that nearly 1/2 of all scientific breast most cancers instances have excessive tiers of stabilized -catenin. In 50% of breast tumors, the effective regulator of Wnt signaling Dvl is increased. Frizzled-associated protein 1 (FRP1), a secreted Wnt inhibitor, become proven to be lacking in seventy-eight percent of malignant breast tumors and become

connected to a negative prognosis. The function of Wnt law withinside the metastatic method of breast most cancers is proven through the downregulation of Wnt inhibitor Dickkopf 1 (DKK1). Furthermore, mutations, lack of heterozygosity, or hypermethylation reason APC expression to be misplaced in 36–50 percent of breast tumors. In basal-like breast cancers, the Wnt/-catenin pathway becomes fantastically energetic, and its nuclear localization becomes connected to a negative prognosis. In vivo studies indicates that activation-catenin now no longer simplest promotes triple-bad breast most cancers, however, it additionally performs a characteristic in HER2-pushed mammary cancers. Because several Wnt ligands can guide the development of breast cancers, restoring many Wnt inhibitors which have been silenced in tumors because of approaches that include tumor growth has been inhibited significantly by DNA methylation and miRNAs. Activation of the Wnt pathway has been demonstrated to increase radiation resistance of progenitor cells in mouse mammary gland and human breast cancer cell lines, implying that Wnt signaling is implicated in anticancer treatment resistance through modulating the population of stem and progenitor cells.

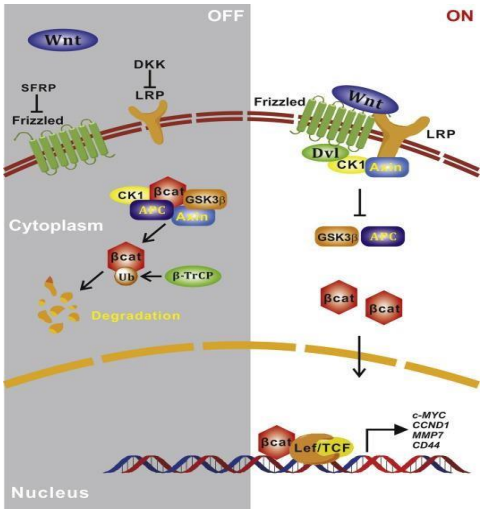

Figure 4: Canonical Wnt/β-catenin signaling pathway. (Feng, Y. et al., 2018) **Cyclin-dependent kinases (CDKs):**

Cyclins, CDKs, and CDK inhibitors all play a function in cell cycle development (CDKIs). To make sure their life, all malignancies provoke the cell cycle. In human breast cancer, overexpression of cyclin D1 and cyclin E, in addition to reduced expression of CDKI p27Kip1, have been located. Amplification of Cyclin D1 is determined in kind of 60% of breast tumors. Furthermore, estrogen's mitogenic movements are mediated through cyclin D1. It turned into located that increased cyclin D1 tumor expression and HER2 overexpression have been

connected to shorter recurrence-loose survival and tamoxifen response. Palbociclib, an oral CDK4/6 inhibitor, turned into proven to inhibit cell cycle development in ER-high quality cell lines, together with people with HER2 amplification. ER-high quality cell lines, together with people with HER2 amplification, have been the maximum touchy to increase inhibition through Palbociclib, whilst nonluminal/basal subtypes have been the maximum resistant.

Breast tumor kinase (BRK): It is a non-receptor tyrosine kinase that is differentially expressed in over 60% of breast cancer patients but not in ordinary mammary glands or harmless lesions. BRK depletion will be studied to see if it can affect EGFR-regulated signaling in breast cancer cells. Stably expressing BRK-Y447F activated BRK, increasing MAPK activity, cell proliferation, and migration in breast cancer cells, even as BRK-depleted breast maximum cancers cells showed a decrease in migration. As a result, BRK may also moreover play an essential characteristic in breast maximum cancers cell proliferation and migration.

PI3K/AKT/mTOR pathway:

In human breast cancers, an oncogenic PI3K mutation (i.e., PIK3CA) can cause luminal or basal mammary progenitor cells to dedifferentiate, allowing them to grow into multi-lineage cells. Hyperactivation of AKT, followed by hyperactivation of downstream mTOR, may result in resistance to endocrine treatments. AKT activation has been connected to worse very last outcomes in patients undergoing endocrine therapy, with patients with a high-quality expression of activated AKT having a lesser therapeutic benefit. The inverse relationship between AKT activation and partial response charges has been discovered. The expression of phosphorylated S6 kinase (S6K), a downstream regulator of mTOR activation, can predict usual survival in patients receiving conventional adjuvant endocrine therapies for hormone receptor-high quality breast cancers. (Feng, Y., et al, 2018).

Some other common signs of breast cancer include:

- Lumps in the breast or underarm region
- Breast length and shape changes
- Pain is a specific region that does not go away.
- Distinguished veins on the breast floor
- Reproductive organ discharge that starts abruptly

- A rash or irritation on the reproductive organ
- Breast swelling, redness, or darkening
- Breast surface roughness of the pores and skin
- Inversion of the reproductive organ or breast distinguishing factors.

In addition, we will say that equal modifications are frequently the result of benign breast conditions. They do now no longer always imply that most cancers are present. However, if someone notices those modifications, he/she ought to see a physician make sure. There are oneof-a-kind forms of breast cancer, and they could affect people in one-of-a-kind ways. Inflammatory breast cancer has particular symptoms. This is an unusual however lethal most cancers that could occur itself in lots of ways. The signs and symptoms are given below:

- Swelling
- Redness
- A bruised, pink, or reddish-purple appearance
- Ridged or honeycombed skin is a type of skin that is ridged or honeycombed.
- In rare cases, a palpable neoplasm can even be a blessing.
- Breast size increases significantly in a short period.
- a feeling of heaviness and discomfort in your breasts
- a method of burning
- The reproductive organ has been turned inside out.
- swollen nodes of body fluid in the arm or underarm

Inflammatory carcinoma develops at a younger age than other cancers. Doctors will misdiagnose it because it might be the result of an illness, trauma, or another issue.

The same symptoms that indicate cancer can also indicate several benign conditions. As a result, it's vital to know which symptoms indicate cancer and which don't.

Risk Factors:

Some people are more likely than others to acquire breast cancer. They should see a doctor if they suffer any of the symptoms described above. According to the American College of Physicians Trusted Source (ACP), the following factors heighten the threat.

- Breast cancer or a high-threat lesion genetic factor, as well as the BRCA 1 or BRCA 2 gene mutation in childhood exposure to chest radiation, are all reported in a circle of relatives. Each scenario could be unique. Knowing about any non-public or personal family history of breast cancer and sharing it with a doctor can help someone notice early warning signs.

1.4 Classification of breast cancer

There are different classification categories for breast cancers. Each scheme uses various criteria to classify tumors and serves a different goal. A few examples are given below:

I. Pathology-based classification

The cellular structure and microanatomy of the cancer are used to classify it. This is the most popular method for classifying or typing breast cancer.

II. Grading system classification

Cancer is classified into numerous grades by the pathologist. A tumor that is "welldifferentiated," for example, has a low grade and seems to be normal tissue. A "poorly

differentiated" tumor is composed of disordered cells that do not match normal tissue and are thus classed as an excessive grade. Other phrases used include "somewhat differentiated" and "medium grade."

III. Based on the stage of cancer:

The stage of cancer is used to classify patients. This is the most widely used method of defining the stage of cancer, and TNM staging considers tumor size, lymph node involvement, and cancer metastasis or dissemination.

IV.Status of proteins and genes:

All breast cancers are now tested for the presence of estrogen receptor (ER), progesterone receptor (PR), and HER2/neu protein expression, as well as any discernible impact. These tests employ immunohistochemistry principles, and once the status of these proteins is known, the prognosis and novel treatments can be determined.

V.Histological findings

The histological appearance of breast cancer is frequently, but not always, used to classify it. The following are examples of histological types:

- **I.** Ductal Carcinoma in situ (DCIS): This shows that the cancer is still in its early stages and hasn't spread. DCIS is a type of early breast cancer that is discovered inside the ductal system and has not spread to the surrounding tissue. It's a type of non-invasive cancer that's rather common.
- **II.** Ductal carcinoma, infiltrating or invasive (IDC): Breast cancer of this sort is the most frequent. It begins in the milk ducts and spreads throughout the body. This can also spread to other parts of the body through lymphatic and circulatory systems.
- **III.** Medullary carcinoma: It is a form of cancer that accounts for around 15% of all breast cancers worldwide. It primarily affects middle-aged women, and the cellular histology is similar to that of the medulla of the brain (gray matter).

IV. Lobular Carcinoma in situ (LCIS): This is a less common form of non-invasive tumor. Most of the time, it does not progress to severe cancer. LCIS is more of a "marker" or early warning sign that breast cancer is on the way. LCIS has recently been renamed lobular neoplasia.

V. Lobular Carcinoma with Infiltrating Carcinoma (ILC): This is the most common type of breast cancer after invasive ductal carcinoma. Cancer begins in the lobules or lobes of the lungs and spreads throughout the body. There is an initial appearance of thickening in the upper-outer portion of the breast. These are frequently estrogen and progesterone receptor-positive and so treatable with hormone therapy.

VI. Tubular carcinoma: It is a form of cancer that originates in cancer cells that look like little tubules. Women over the age of 50 are at a higher risk of developing this type of breast cancer. This tumor's treatment is effective.

VII. Mucinous carcinoma or colloid carcinoma: This is a rare type of invasive breast cancer that only occurs in a small percentage of cases. Cancer cells create mucus, which may be separated from normal cells under a microscope. When mucus and cancer cells combine, they generate tumors that resemble jelly.

VIII. Paget's disease: It is a disorder that affects people's nipple skin and causes them to develop an eczema-like appearance. The nipple has itchy, scaling, and seeping discharge. Breast cancer affects 90% of women who experience these symptoms.

Paget's Disease can attack at any age, but women are more likely to be affected.

IX. Inflammatory breast cancer: This is a rare type of breast cancer that is also quite aggressive. The malignancy causes the lymph veins in the breast skin to become blocked. Instead of a lump, cancer looks to cover a huge portion of the breast, like a sheet. Swollen, red, and inflammatory breasts are visible.

X. Triple-negative breast cancer: The estrogen receptor (ER), progesterone receptor (PR), and HER2/neu proteins are all negative in this breast carcinoma.

XI. Metastatic breast cancer: Breast cancer has progressed to the point where it has spread to other organs such as the liver, brain, and bones.

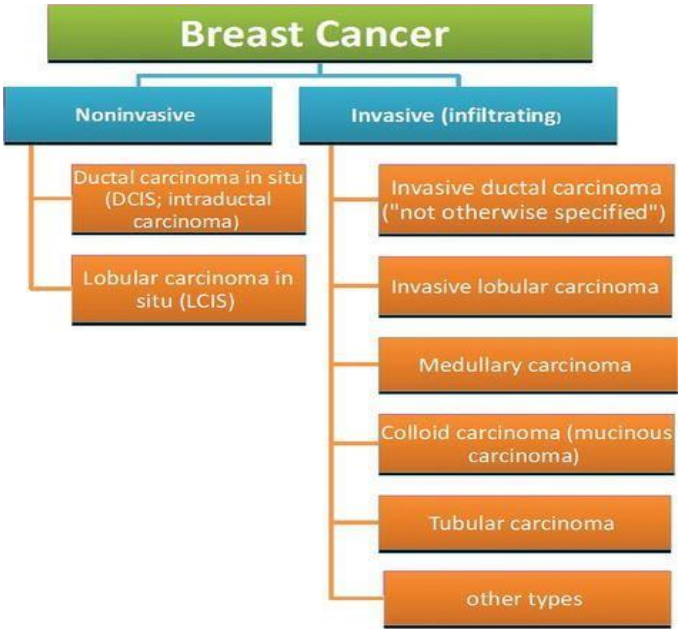

Figure 5: Classification of Breast Cancer (Kamel, H. et al., 2017)

1.5 Clinical breast exam/ diagnosis of breast cancer

Diagnosis of breast cancer can have several stages tests like screening tests, diagnostic tests, and monitoring tests. A clinical physical examination is no longer recommended as part of routine screening, according to the ACP recommendations. If a person senses a change, a doctor may do a physical examination and after that several diagnostic tests must be given to get the proper idea of cancer.

In the physical examination the doctor may next perform one of the following procedures:

- Visual inspection: They will ask the patient to lift and drop their arms to check for variations in breast size and shape. They'll search for rashes, dimpling, and nipple discharge, among other things.

- Manual examination: The doctor will evaluate the entire breast, underarm, and collarbone with the pads of their fingertips for any anomalies or suspicious tumors. They will also look for enlarged lymph nodes. Any changes or unusual characteristics will be recorded by the doctor, who may order additional tests.

Further tests include:

Mammogram: A mammogram is a sort of ray this is used to study the breast. Breast most cancers screening is regularly finished thru mammograms. If a screening mammogram wellknown shows an abnormality, your medical doctor may also endorse a diagnostic mammogram to research similarly.

Ultrasound of the breasts: Ultrasound imaging creates pictures of systems deep inside the frame through the use of sound waves. A new breast lump may be identified via way of means of ultrasound to peer if it is a stable mass or a fluid-stuffed cyst. This does now no longer contain radiation and can display an extra element than a mammogram or verify the outcomes of a mammogram.

Biopsy: A medical doctor uses a needle or another tool to extract tissue or fluid from the area in preparation for similar tests. Taking a biopsy of a breast cell pattern (biopsy). Breast cancer can only be diagnosed definitively by a biopsy. During a biopsy, the doctor takes a sample of tissue from the suspected spot using a specialized needle tool guided by an X-ray or other imaging test. A small metallic marker is frequently put on the site inside your breast so that subsequent imaging exams may easily identify the area.

Biopsy samples are sent to a facility for examination, where professionals determine whether or not the cells are cancerous. A biopsy pattern is also assessed to determine the type of cells involved in breast cancers, the aggressiveness (grade) of cancer, and whether or not the cancer cells have hormone receptors or other receptors that affect the aggressiveness of cancer (grade).

MRI: This could provide a detailed view of the breast. Using a magnet and radio waves, an MRI machine creates images of the interior of your breast. Before the breast MRI, the patient will be given a dye injection. Unlike other types of imaging treatments, an MRI does not use radiation to create images.

To stage breast cancer, blood tests such as a complete blood count, a Mammogram of the other breast to screen for cancer signs, a Breast MRI, Bone scan, Computerized tomography (CT)

scan, Positron emission tomography (PET) scan, and other tests and procedures may be utilized.

It is not a sign that a person has breast cancer if a doctor suggests this testing. The results will often reveal that there is no malignancy. (Tom Seymour, 2019)

1.6 Prevalence of breast cancer

Breast cancer claimed the lives of 684,996 people worldwide in 2020. (WHO, 2021). Breast cancer will kill 43,250 women and 530 men according to the estimation in 2022. (ACS, 2022). In the United States, an estimated 3.8 million people were living with a history of breast cancer in 2019. (DeSantis et al., 2019). In 2017, 155,000 women in the United States were living with metastatic breast cancer, and 168,292 by 2020. (Mariotto et al., 2017)

In 2019, around 268, 600 new cases of invasive breast cancer and 48, 100 new cases of DCIS are expected to be diagnosed in the United States, with 41,760 women dying from the disease. Eighty-two percent of women over 50 are diagnosed with breast cancer, and ninety percent of breast cancer deaths occur in this age group. The median age of women having cancer in their breasts at the time of analysis was sixty-two years, with black women (60 years) marginally

younger than white women (sixty-three years). Breast cancer death occurs at an average age of 68 years for all women, 70 years for white women, and 63 years for African-American women. (Simon, A., & Robb, K,2021).

Table 1: Estimated New Ductal Carcinoma In Situ and Invasive Breast Cancer Cases and Deaths Among Women by Age, United States, 2019

AGE, Y	DCIS CASES		INVASIVE CASES		DEATHS	
	NO.	%	NO.	%	NO.	%
<40	1180	2%	11,870	4%	1070	3%
40-49	8130	17%	37,150	14%	3250	8%
50-59	12,730	26%	61,560	23%	7460	18%
60-69	14,460	30%	74,820	28%	9920	24%
70-79	8770	18%	52,810	20%	8910	21%
80+ **All ages**	2830	6%	30,390	11%	11,150	27%
	48,100		**268,600**		**41,760**	

1.7 Aims and objectives

The purpose of this review paper is to learn more about a specific type of breast cancer known as triple-negative breast cancer, as well as treatment options. The other objectives are to create awareness among the public about these particular types of breast cancer so that whenever they feel some kind of abnormality it can be diagnosed in time and can start the treatment and also to aid in research and to develop interest so that the scientists do more research on this type of cancer and may invent new strategies of treatment.

Chapter 2 Research Methodology

A thorough literature overview was accomplished to obtain all of the data used in this review paper. The data was gathered from diverse credible sources, which consist of peer-reviewed journals, and online scholarly databases. Following is the listing of a number of the various databases that have been searched significantly for the existing study.

I. Journal Database
II. Library Catalogue
III. Newspaper Database
IV. Professional website
V. Books

Chapter 3 Triple Negative Breast Cancer

3.1 What is triple-negative breast cancer?

TNBC (triple-negative breast cancer) is characterized as 1% estrogen receptor (ER) positive tumor cells, PR negativity, and daily HER2-receptor evaluation by immunohistochemistry (IHC) or in situ hybridization (ISH) independently or in combination. In the literature, TNBC and basal-like breast cancers are widely used interchangeably; however, the two designations will not be used interchangeably because basal-like breast cancers may be receptoradvantageous in rare cases. TNBC accounts for 15–20 percent of all breast cancers. Because of enhanced competitive medical behavior and a lack of molecular targets for therapy, TNBC affects more young women and has a worse prognosis than breast cancer in general. (Stovgaard, E. S., et al., 2017).

TNBC (triple-negative breast cancer) is more frequent in women under the age of 40 than hormone-positive breast cancer. The histology is typically high-grade, with surrounding necrosis, a pushing invasion border, and a stromal lymphocytic response, and is classed as infiltrating ductal carcinoma. In terms of medical outcomes, TNBC is more competitive than other forms of breast cancer, with a significant chance of relapse, a short progression-free survival (PFS), and short overall survival (OS). After surgery, half of the patients with earlystage TNBC (levels I to III) have disease recurrence, and 37% die within five years. (Lee, K.L., et al, 2019)

3.2 Diagnosis and survival rate of TNBC

Breast cancer cells can be screened for specific proteins after a diagnosis has been made using imaging tests and a biopsy. The malignancy is categorized as triple-poor if the cells lack estrogen or progesterone receptors (ER or PR) and no longer produce any or an excessive amount of the HER2 protein. TNBC is classed as a competitive disease because it spreads quickly, is more likely to be advanced by the time it is identified and relapses more frequently after therapy than other types of breast cancer. The analysis isn't as precise for this type of breast cancer as it is for others. The percentage of persons with the same type and stage of cancer who are still alive after a particular amount of time (typically five years) after being diagnosed is referred to as the survival rate. They can't tell you how long you'll survive, but they can tell you how likely your treatment is to work.

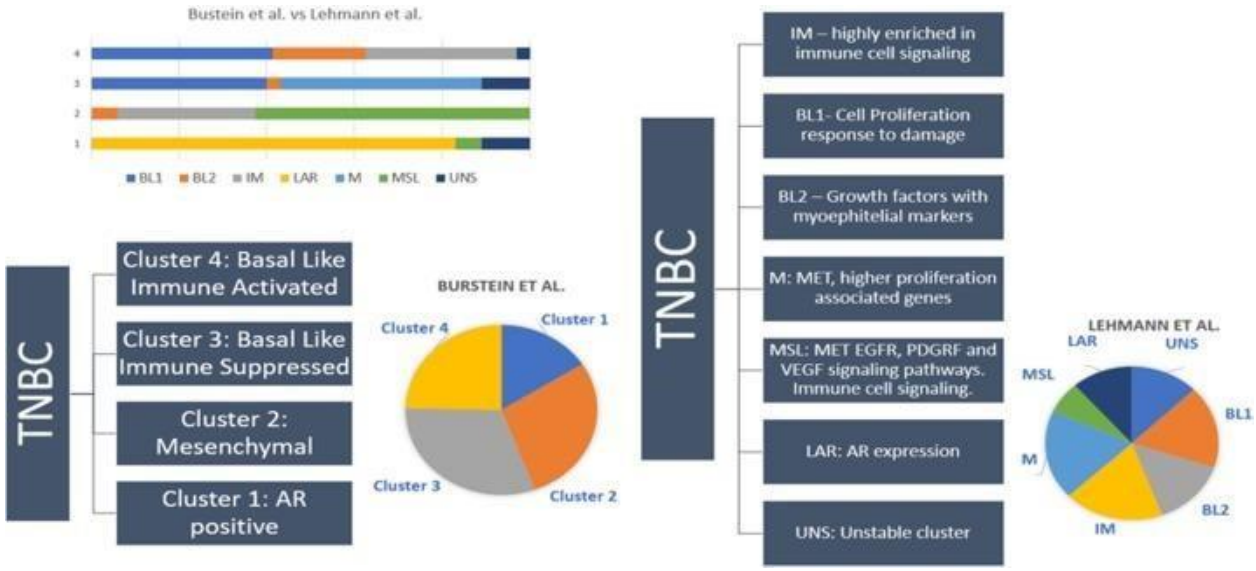

Figure 6: Clusters of triple-negative breast cancers. (Silva, J. L., et al, 2020)

3.3 Biomarkers

TNBC is distinguished by the presence of positive biomarkers. Although such chemicals are not always limited to TNBC, they appear to be more common in this subtype. TNBC's basic biomarkers are as follows:

EGFR: EGFR is one of four closely similar receptors, each with a unique role in tumor cell survival. EGFR (or ErbB-1), HER-2/neu (ErbB-2), HER-3 (ErbB-3), and HER-4 are the four receptors (ErbB-4). Following ligand activation and TK, the inactive monomer receptor dimerizes, and the intracellular portion of the receptor is activated via autophosphorylation, leading to a cascade of intracellular processes. The EGFR signaling system influences cell proliferation, angiogenesis, metastatic dissemination, and apoptosis suppression. TNBCs that explicit EGFR offers a tremendous remedy challenge. Variable EGFR expression has been recognized in metaplastic breast cancers, and phenotypes of BLBCs, in research the usage of numerous strategies of gene amplification. TNBCs, on the alternative hand, show off excessive EGFR gene replica levels, in line with real-time polymerase chain reactions. EGFR expression is found in forty percent to 50 percent of breast most cancers sufferers and eighty percent of TNBC and is notion to update major breast most cancers proliferation pathways generated via way of means of activation of HER-2, ER, and PR proteins, that are missing in TNBC. The authors located that 60 percent of sufferers with grade III cancers and greater than 3 lymph nodes had EGFR expression, implying that EGFR expression is related to the disease's aggressiveness. They additionally concluded that sufferers with EGFR expression had decreased DFS, DDFS, OS, and cause-precise survival. TNBC with excessive EGFR expression has a terrible reaction to remedy. On the other hand, EGFR expression was detected in 24% of TNBC patients and was linked to a poorer response to chemotherapy and survival, whereas EGFR expression was linked to a better response to chemotherapy and survival within the luminal groups. EGFR is now defined alongside other markers to distinguish the BL subtype from TNBC. This permits TNBC to be classified into subtypes based on the identity of prognostic variants and molecular targets. According to research, non-uniformity in expression styles is caused by a loss of subtype attention or BL subtype no segregation from central TNBC. As a result, EGFR has been identified as a biomarker in TNBC and as a target for the TK inhibitor cetuximab. Many investigations have been conducted to investigate how it reacts in TNBC. In a recent study, EGFR expression was revealed to be a prognostic factor for DFS, not only in univariate but also in multivariate analysis.

Vascular endothelial growth factor: Angiogenesis is vital for tumor growth and dissemination, particularly on the far side of a two-millimeter diameter, because elements and nutrition cannot go beyond this distance. Tube epithelium protein transmits angiogenic signals that aid neovascularization (VEGF). A set of six macromolecules known as VEGF A, B, C, D, E (viral factor), and placental growth factor. Because of alternate splicing of its mRNA, the VEGF protein occurs in four isoforms. The 165-amino-acid molecule is relatively common among the several VEGF165 isoforms. Variables that affect its sequence expression include hypoxia, chemical element oxide, growth factors, oncogenes, tumor suppressor genes, and HER-2.

It promotes epithelium cell proliferation whereas protecting their structural and useful integrity. It additionally controls the porousness of blood vessels and therefore the migration of endothelial stem cells from the bone marrow. VEGF regulates neovascularization in neoplasms by boosting the assembly of anti-apoptotic proteins equivalent to Bcl2, XIAP, and surviving. epithelium cells suffer programmed cell death within the absence of it, and newly created vasculature disintegrates. As a result, VEGF expression is needed for neovascularization throughout tumor growth. VEGF interacts with a range of receptor TKs, as well as VEGFR-1, VEGFR-2, and VEGFR-3. development is triggered by VEGF binding to VEGFR-2, which activates bound TKs, which then starts numerous signaling cascades that result in endothelial cell survival, proliferation, migration, adhesion, actin remodeling, and vascular permeability. In DCIS and invasive breast cancer, VEGF expression is increased. It's also been used to predict the prognosis of breast cancer patients. Its measurement in tissue extracts by IHC or ELISA has revealed a substantial correlation with microvessel counts or density. Because high mean vascular density is connected to more aggressive tumor behavior and poor survival in breast cancer, intertumoral microvessel density is now regarded as one of the most critical determinants impacting survival. According to current research, there is a direct link between VEGF levels in serum and tissue and grade III tumors, bigger tumor size, positive lymph node and negative hormone status, and poor survival, as well as a significant decrease in levels after treatment. Higher VEGF levels in TNBC are linked to a shorter DFS and OS. Higher VEGF levels in TNBC are linked to shorter DFS, OS, and DDFS. VEGF levels have also been found to be linked to tumor size, grade, and metastatic areas. The disease progressed despite treatment in patients with greater VEGF levels, and these patients had a considerably poorer progressionfree survival rate than those with lower levels. When TNBC patients were given FAC, VEGF levels increased significantly from baseline to the middle of the therapy but did

not increase significantly from midway to the end of the therapy. In TNBC patients, bevacizumab targets VEGF.

C-kit and basal cytokeratin: The cytokine receptor C-kit can be found on the surface of hematopoietic stem cells and other cells. C-kit is a growth factor receptor that binds to the stem cell factor and enhances key physiological processes such as cell survival, proliferation, differentiation, adhesion, and chemotaxis. It causes cancer cells to apoptosis and increases their invasiveness, causing them to perish. CKs are intermediate filament keratin-containing proteins present in epithelial tissue's intracytoplasmic cytoskeleton. At various stages of development and final differentiation, distinct epithelial tissues express different CKs. This variation in CK expression aids in epithelia categorization. Distinct tumors express different CKs from that epithelium. As a result, when an epithelium goes through a malignant transformation, the CK expression profile tends to stay steady. For tumor pathologic classification, the use of IHC techniques to assess the CK profile is crucial. These CKs were initially utilized to differentiate between malignant and benign breast lesions, but their prognostic relevance was discovered later, with CK-5, CK-14, and CK-17 expression associated with poor prognosis, high-grade tumors, ER-negative, short DFS, and OS. It is written in BLBCs. Because BLBCs and TNBC have similar characteristics, C-kit and basal CKs, as well as other markers and clinical abnormalities, are used to differentiate them.

P53: The TP53 gene produces the p53 tumor suppressor protein (the tumor suppressor gene). Because it controls the cell cycle, it's also known as the "guardian of the genome". It promotes chromosomal stability and governs cell development, multiplication, proliferation, and apoptosis. Carcinogenesis occurs when these functions are disrupted by a mutation in the p53 gene. Many pathways depend on different upstream regulatory kinases to activate p53 in response to cellular stress. First, mutant proteins produced in response to the DSB, second, a pathway dependent on the INK4 gene product, p14ARF activated by oncogenes, and third, a mechanism induced by chemotherapeutic medications and ultraviolet radiation that is independent of the above two processes. In 18% to 25% of primary breast carcinomas, p53 mutations are found. The gene p53 is involved in the prognosis of breast cancer. Chemotherapy responsiveness is hampered by p53 overexpression. Its activation has been linked to an aggressive form of breast cancer in many studies, and it has been shown to reduce DFS and OS in TNBC patients. Furthermore, co-existence with HER-2 was linked to an increased risk of

early relapse and death after surgery. It is utilized to separate a subtype, such as basal-like from core TNBC, along with EGFR and cytokeratin. P53-mutated tumors are highly invasive, poorly differentiated, and high-grade cancers. In TNBC patients, a p53 mutation was linked to a poor response to chemotherapy, according to a study.

TOP-2A: This gene codes for topoisomerase II, which is important for DNA transcription. This enzyme breaks double strands of duplex DNA temporarily and rejoins them so that the strands cross through one another, changing the architecture of DNA. Cancer mutations result in a loss of function and, as a result, a deterioration of the situation. The gene works as a target for anthracycline therapy, which is a topoisomerase II inhibitor, in TNBC or breast cancer. As a result, it serves as a marker for assessing anthracycline resistance. TOP-2A expression was shown to be greater in 2.7 percent to 8.8 percent of TNBC patients in a study. Its overexpression in TNBC causes a decrease in anthracycline sensitivity and, as a result, a decrease in response. (Yadav, B. S., Chanana, P., & Jhamb, S. 2015).

Table 2: Biomarkers for Prognosis and Prediction in Triple-Negative Breast Cancer (Sukumar, J., et al, 2021).

Biomarker	Approximate Prevalence in TNBC	Mechanism	Targeted Therapy	Prognostic/Predictive Significance
BRCA 1/2 germline mutation	10–20%	Repair of DNA double-strand breaks and homologous recombination	PARP inhibitor	Higher platinum reaction and predictor of PARP inhibitor response
Elevated HRD score	45–70%	Repair of DNA double-strand breaks and homologous recombination	There is no clinically useful targeted treatment.	PCR predictor of neoadjuvant platinum therapy
PDL1	Variability (immune vs tumor), disease stage, antibody: 40% on immune cells (SP142 antibody) in metastatic disease 80% by CPS ≥1 (22C3 antibody) in primary disease	Tumor immune surveillance evasion	Immune checkpoint blockers	Improved PCR and survival in immunotherapy trials
Tumor-infiltrating lymphocytes	Variability (intra-tumoral vs stromal, primary vs metastatic)	Infiltration of the tumor microenvironment by stromal lymphocytic cells	There is no clinically useful targeted treatment.	Improved PCR, DFS, and OS in patients with early TNBC; a predictor of greater response to neoadjuvant CT
High tumor mutational burden	3–11%	The number of somatic mutations per megabase of DNA	Pembrolizumab	Pembrolizumab response predictor
MSI-H/ MMR	<2% of all breast cancer	Errors in DNA replication caused by flaws	Pembrolizumab	Pembrolizumab response predictor
AR	30–35%	Nuclear transcription factors derived from steroids	Abiraterone Acetate Bicalutamide Enzalutamide	DFS improvement; may be related to chemoresistance

EGFR	13–76%	Tyrosine kinase receptor involved in cell proliferation/survival	There is no clinically useful targeted treatment.	Poor prognostic variables are linked to a lower DFS.
VEGF	30–60%	Promote angiogenesis by binding to receptor tyrosine kinases.	There is no clinically useful targeted treatment.	High levels of expression are linked to disease progression and metastasis.
HER2	45–55% of all BC with HER2 IHC 1+ or 2+ 2% of BC with HER mutation	HER2 protein expression is low, while ERBB2 gene amplification is undetectable.	Anti-HER2 TKI antibodydrug conjugates vaccinations for HER2mutated patients	Response to HER2antibody-drug conjugate and TKIs may be predicted by this factor.
TP53 mutation	80%	This gene encodes a transcription factor protein that induces cell cycle arrest.	There is no clinically useful targeted treatment.	There are conflicting accounts on the predictive relevance
MicroRNAs	N/A	Noncoding RNAs control the posttranscriptional expression of genes implicated in cancer development.	There is no clinically useful targeted treatment.	Signatures linked with poor DFS, poor OS, and chemoresistance
PI3K/AKT/mTOR pathway	*PI3K* 7–9% *PTEN* 30–50%	PI3K - intracellular lipid kinases that participate in a signaling cascade that promotes cell growth and survival.	Alpelisib Ipatasertib Capivasertinib	Potential determinants of PI3K/AKT/mTOR inhibitor response
NTRK gene fusion	<1%	PTEN is a tumor suppressor gene that inhibits the signaling cascade.	Larotrectinib Entrectinib	Predictor of tropomyosin receptor kinase inhibitor responsiveness

3.4 Therapeutic targets

Drugs that target specific elements of cancer cells, such as proteins or genes, that help tumors grow and spread, are known as targeted cancer therapies. They may also target other types of cells that aid in the growth and spread of cancer. Targeted therapy may be more effective than other treatments for some forms of cancer. The FDA has approved targeted therapy for over 15 cancers, including breast, prostate, colon, and lung cancers. However, they are only effective if your tumor has the correct target. Additionally, targeted therapies can stop functioning if the target changes or if your tumor develops a resistance to the treatment.

Researchers are gaining a better understanding of the alterations that lead to cancer. This could lead to more precise treatments in the future.

Some targeted therapeutic strategies for Triple-Negative Breast Cancer are given below:

- Inhibition of Poly (ADP-ribose) Polymerases in TNBC
- Inhibition of Immune Checkpoints in TNBC
- Application of Antibody-Drug Conjugates in TNBC
- Inhibition of Signaling Pathways in TNBC
- Inhibition of Angiogenesis in TNBC
- Inhibition of Epigenetic Modifications in TNBC
- Inhibition of Cell Cycle in TNBC (Li, Y et al.,2021)

Chapter 4 Treatment and potential drugs

4.1 Current treatment options

As there are fewer specific treatments available to treat triple-negative breast cancer, it is thought to be more aggressive and has a worse prognosis than other kinds of breast cancer. Triple-negative breast cancer has been demonstrated in studies to be more likely to spread outside the breast and to recur (come back) after therapy. It has a higher prognosis than other forms of breast cancer. In terms of appearance and growth patterns, the higher the grade, the fewer cancer cells resemble normal, healthy breast cells. Triple-negative breast cancer is frequently graded 3 on a scale of 1 to 3.

Clinicopathological parameters such as patient age, TNM (tumor size, lymph node status, metastasis), stage, tumor grade, histology, and molecular subtype of breast tumors are commonly used to aid medical decision-making in the selection and prescription of effective treatment regimens at the time of diagnosis. The American Joint Committee on Cancer (AJCC) introduced prognostic biomarkers to the usual anatomic staging classification in TNBC in its ninth edition to improve precision medicine. When weighing the risks and benefits of treating early-stage and low-risk TNBC, various criteria must be considered when designing the best treatment sequencing and therapeutic combinations. Overtreatment can result in chemotoxicity with no benefit, whereas undertreatment can result in relapse and poor outcomes. Overtreatment can cause chemotoxicity without providing any benefit, whereas undertreatment can lead to recurrence and poor outcomes. TNBC is high-risk and locally progressed, on the other hand, requires rigorous treatment using a variety of chemotherapy regimens and medication combinations. Since cytotoxic chemotherapy is typically the sole systemic option for treating TNBC to decrease and avoid tumor relapse and systemic metastasis, the great majority of TNBC patients with high-risk and locally progressed cancer have little alternative but to continue with the chemotherapies.

Ineffective or toxic chemotherapy increases the treatment burden and frequently causes unpleasant side effects and long-term adverse health implications, lowering the patient's quality of life.

Several types of treatment options are included below:

I. **Neoadjuvant Therapy:** Chemo-resistance is a major issue for oncologists nowadays, accounting for up to 90% of medication failures in metastatic cancers. Patients with TNBC initially respond well to neoadjuvant therapy. Patients exhibited a higher risk of relapse in the first five years when compared to other cancer subtypes. Despite this, neoadjuvant chemotherapy is the gold standard treatment for TNBC. It is vital to be vigilant in TNBC patients; nonetheless, proper treatment selection increases the prognosis. Furthermore, despite recent reports of resistance to these medicines, neoadjuvant anthracycline–cyclophosphamide (AC-scheme) chemotherapy appears to be gaining traction. In the presence of BRCA mutations, Scheme AC, which comprises Doxorubicin and Cyclophosphamide for 4 weeks followed by Paclitaxel for 12 weeks, has a pathological complete response (PCR) rate of 27–30%. If they combine drugs like Cisplatin, the prognosis could improve to 61%. Other drugs that can be used include carboplatin (CALGB40603), Abraxane (Nab-Paclitaxel nanoparticles), and Bevacizumab. To monitor the disease after treatment, imaging methods like MRI, which is the most sensitive imaging modality for monitoring TNBC neoadjuvant response therapy, should be used. Precision medicine identifies critical indicators in each oncology patient, allowing for more effective and targeted chemotherapy. According to medical research on the fringes of personalized medicine, EGFR, which is favorably expressed (about 60%) in TNBC, is one of the most useful molecular targets for TNBC treatment. Because cisplatin is shown to be effective in TNBC in preoperative phase II studies where BRCA-1 expression is absent, neoadjuvant treatment boosts the response rate in TNBC patients compared to adjuvant therapy. Although BRCA-1-mutated tumors are basal, not all basal malignancies express the mutation, neoadjuvant systemic therapy should be individualized to each patient. Furthermore, as experts point out in meta-analyses, E2100, AVADO, RIBBON-1, cisplatin, and bevacizumab, the most recent molecular target of VEGF, are effective drugs in neoadjuvant therapy against TNBC. In vitro studies have revealed that malignant cells with the BRCA-1 mutation are resistant to taxanes, while a clinical trial called "CALGB9344/INT1048" discovered that utilizing paclitaxel reduces cancer recurrence by 17 percent and the risk of mortality in 18 percent of TNBC patients.

II. **Adjuvant Therapy:** Adjuvant therapy is also critical for preventing metastases, fast tumor advancement, and recurrence activity. According to the MA5 study,

anthracycline-based therapies are ineffective when BRCA-1 is present in TNBC, however, anthracyclines have shown potential as adjuvant treatments in other studies. To establish whether adjuvant therapy is appropriate for each patient, a detailed analysis of clinical-histopathological staging circumstances and an acceptable categorization of genomic and proteomic profiles should be used. TNBC has already been addressed as having the ability to spread, and the presence of significant tumor stroma has been associated with shorter survival duration. As a result, in a palliative condition, it is critical to examine the chemotherapy regimen since the practitioner must be aware of what is going on. Many clinical trials are being conducted to determine the optimal treatment for TNBC, such as comparing carboplatin efficacy in metastatic TNBC versus docetaxel efficacy. Despite the use of various taxane dosages in metastatic breast cancer (MBC), no indication of efficacy in TNBC has been found. When anthracyclinetaxanescheme resistance is documented in advanced stages (III C), XelodaTM (Capecitabine) coupled with TaxotereTM (Docetaxel) is given intravenously. IxempraTM (Ixabepilone) with Capecitabine is another effective combination, while IxempraTM can also be administered alone at the same dose.

III. **Surgery:** There has been a lot of research done to see how mastectomy compares to lumpectomy in terms of prognosis. Patients are still candidates for breast conservation because the surgical therapy of choice has no effect on prognosis or local tumor recurrence in TNBC. A lumpectomy followed by radiation therapy may be an option (National Comprehensive Cancer Network guidelines). However, in the event of TNBC, neoadjuvant therapy is the gold standard and is recommended before surgery.

IV. **Radiotherapy:** TNBC treatment may include radiotherapy as well as conservative breast surgery, but this is debatable. TNBC-BRCA-1 atypical expression, on the other hand, appears to be extremely radiosensitive, based on evidence. TNBC is a disease that can be cured by radiation. Unfortunately, there are no treatment guidelines for the use of RT in TNBC, unlike for pharmacological treatment. (Medina et al., 2020).

V. **Immunotherapy:** Immunotherapy has been found to improve survival in other solid tumors, thus it could be a viable treatment choice for TNBC. Immune checkpoint inhibitors (ICIs), which improve the cytotoxicity and proliferative potential of tumorinfiltrating cells by targeting immunosuppressive receptors including CTLA-4 and PD1, are the most effective immunotherapeutic drugs (TILs). TNBC is more likely than other breast cancer subtypes to react to immunotherapy due to several factors. TNBC, for example, has more TILs than other tumors, which correlates with larger ICI responses in other cancers, and high TIL levels in TNBC are connected to a better prognosis in early-stage TNBC. Second, TNBC has higher PD-L1 expression on tumor and immune cells, making it a direct target for ICIs and correlating with anti–PD-1 therapeutic response in other malignancies. Finally, TNBC has more nonsynonymous mutations, which produce tumor-specific neoantigens, which activate neoantigenspecific T cells, resulting in an anticancer immune response that can be increased by ICIs. (Li, Y et al., 2020)

4.2 Approved drugs and potential drugs

Patients with metastatic triple-negative breast cancer have a poor prognosis. Sacituzumab govitecan is an antibody-drug combination that consists of an antibody that targets the human trophoblast cell-surface antigen 2 (Trop-2) protein, which is found in the vast majority of breast cancers, and a novel hydrolyzable linker that binds it to the SN-38 protein (topoisomerase I inhibitor). 468 individuals with no brain metastases were randomly assigned to either

sacituzumab govitecan (235 patients) or chemotherapy (232 patients) for statistical analysis (233 patients). The patients were all 54 years old and had used taxanes previously. The median progression-free survival with sacituzumab govitecan was 5.6 months (95 percent CI, 4.3 to 6.3; 166 events), compared to 1.7 months with chemotherapy (95 percent CI, 1.5 to 2.6; 150 occurrences) (hazard ratio for disease progression or death, 0.41; 95 percent CI, 0.32 to 0.52; P0.001). The median overall survival with sacituzumab govitecan was 12.1 months (95 percent confidence interval: 10.7 to 14.0), compared to 6.7 months with chemotherapy (95 percent CI: 5.8 to 7.7). (Hazard ratio for death: 0.48; 95 percent confidence interval: 0.38 to 0.59; P0.001). The proportion of patients who achieved an objective response to Sacituzumab go-vegan was 35%, compared to 5% with chemotherapy. Neutropenia (51 percent with Sacituzumab novicecan and 33 percent with chemotherapy), leukopenia (10 percent and 5%), diarrhea (10% and 1%), anemia (8 percent and 5%), and febrile neutropenia were the most common grade 3 or higher treatment-related adverse effects (8 percent and 5 percent). (6% and 2%, respectively). In each group, three patients died as a result of adverse events; no deaths were attributed to the use of sacituzumab govitecan. (Bardia et al., 2021).

4.3 Limitations of current therapies

In terms of outcomes, the translation of PCR into a favorable prognosis is obvious in triplenegative and HER2-positive patients; however, it is more difficult to demonstrate in other subtypes, such as HR-positive patients with a grade of 1 or 2. These individuals are difficult to treat since they have a decent prognosis but frequently do not react to chemotherapy. Novel molecular diagnostics may aid in identifying individuals who have a good prognosis and hence do not require chemotherapy. Because of the low response rates in HR-positive, and HER2negative patients, neoadjuvant chemotherapy has been focused on triple-negative and

HER2positive patients, with some trials enrolling only those two groups. (Fasching, et al., 2016).

Acute side effects of adjuvant chemotherapy include nausea, vomiting, hair loss, myelosuppression, early (but not long-term) cognitive impairment, and amenorrhea. Chemotherapy-induced immunosuppression can lead to serious infections in certain people. Taxanes cause neuropathy, which usually goes away within a few weeks to months of treatment but can be incomplete in severe cases.

If microscopic illness surrounding the borders of the tumor cannot be killed, tumor cells may remain in the patient after surgery. The patient must be able to endure the operation and anesthesia (i.e., have few medical problems, adequate lung function, and not be on specific drugs), as well as some damage to normal tissues in the region. Surgery-related complications (e.g., infection, and others that are site-specific). The removal of an organ in this case breast may hurt the patient's quality of life.

Radiation not only kills or delays cancer cells, but it also has the potential to harm healthy cells in the vicinity. Healthy cells can be damaged, which might have negative repercussions. Many people experience fatigue as a result of radiation therapy. Fatigue is a feeling of being tired and worn out. It can happen all at once or over time. People experience fatigue in different ways, and someone getting the same amount of radiation therapy to the same body location may feel more or less tired.

Immunotherapy is not an option for all patients with triple-negative breast cancer because immune checkpoint inhibitors like atezolizumab and pembrolizumab interfere with the connection between PD-1 and PD-L1, therefore they're currently exclusively used to treat triple-negative breast cancer patients who have the PD-L1 protein on cancer cells and/or immune cells within the tumor. An immunohistochemical test is used to see if a patient has a high level of PD-L1 expression. This procedure is carried out on tissue that has been extracted during a biopsy. PD-L1 immune checkpoint inhibitors will not work if the PD-L1 protein is not detected on cancer cells and/or immune cells within the tumor.

Secondly, these medications are only approved for people with advanced diseases at this time. After initial therapy, cancer must have returned and become ineligible for surgery, or it must have spread to other regions of the body.

4.4 Limitations of drugs

For people taking sacituzumab govitecan, the following adverse effects are common (occurring in more than 30% of cases):

I. Low white blood cell counts that are severe or life-threatening **II.** Diarrhea

III. Vomiting and nausea

IV. Red blood cell levels are low.

V. Hair loss is a common problem.

VI. Constipation

VII. Rash

VIII. Appetite decreases

Chapter 5 Future studies

The US Food and Drug Administration (FDA) approved Keytruda (chemical name: pembrolizumab) combined chemotherapy before surgery, followed by Keytruda alone after surgery, on July 26, 2021, to treat triple-negative breast cancer in its early stages with a high chance of recurrence Keytruda is an immune checkpoint inhibitor used in immunotherapy. Before it can mount an immunological response to a foreign invasion, the immune system must be able to distinguish between "self" (part of you) and "non-self" (not part of you) cells or substances (not part of you and possibly harmful). Your immune system recognizes your body's cells as "self" by looking for proteins on their surfaces or inside them.

Immune checkpoints are proteins that allow our immune system to detect the difference between "self" and "non-self" cells. Cancer cells have been shown to use immune checkpoint

proteins as a barrier to avoid being recognized and killed by the immune system. T cells are immune system cells that look for indicators of disease or infection in the body. When T cells come into contact with another cell, they look for certain proteins on its surface that will assist them in recognizing it. If the surface proteins of the cell indicate that it is normal and healthy, the T cell will ignore it. If the surface proteins of the cell indicate that it is normal and healthy, the T cell will ignore it. The T cell attacks the cell if the surface proteins on its surface indicate that it is malignant or otherwise ill.

The FDA authorized the combination of Keytruda and chemotherapy in 2020 for the treatment of unresectable locally advanced or metastatic triple-negative, PD-L1-positive breast cancer that is unresectable locally advanced or metastatic. Unresectable cancer cannot be removed through surgery.

The drug decitabine, which is already approved to treat myelodysplastic syndrome, was identified by Mayo Clinic researchers to be effective in treating triple-negative breast cancer, which is one of the most aggressive and deadly types of breast cancer.

According to Houston Methodist researchers who announced results on a new combined therapy with the potential to enhance outcomes for these difficult-to-treat breast cancer patients, a medicine used to treat heart failure has shown encouraging results in treating triplenegative breast cancer.

A research team led by Jenny Chang, M.D., a breast medical oncologist and director of the Houston Methodist Dr. Mary and Ron Neal Cancer Center, uncovered variants in the RPL39 gene that works through the nitric oxide pathway. Using a combination of chemotherapy and L-NMMA, a nitric oxide synthase inhibitor developed at Houston Methodist, researchers were able to slow tumor development and prevent the spread of triple-negative breast cancer. In the past, patients with chemotherapy-resistant cancers had a 25-30% probability of responding to older immune-system-targeting drugs. L-NMMA, a medication discovered by Houston Methodist, has a response rate of roughly 50%. This study relies on prior Houston Methodist research that discovered a gene mutation that causes a chemical that inhibits triple-negative breast cancer, as well as the most aggressive type of triple-negative breast cancer. (Henderson, 2021)

Chapter 6 Conclusion

As triple-negative breast cancer lacks receptors that can be addressed with pharmacological therapy, differs from other kinds of breast cancer. Breast cancer cells can have three types of receptors: estrogen, progesterone, and a protein called HER2, each of which acts as a lock on a front door. The many hormonal or pharmacological therapies that can get entrance and kill cancer cells are the keys to these locks. However, triple-negative breast cancer lacks all three types of receptors, therefore the term. As a result, treatment for this type of breast cancer is more complicated than for other types of breast cancer. Triple-negative breast cancer, according to specialists, can be a relatively controlled and potentially curable type of cancer, especially with recent scientific developments. Triple-negative breast cancer treatment includes both local and systemic therapy, such as surgery and radiation. Another class of treatments, known as immunotherapy, is now accessible as a result of recent research, in which medicines help boost the immune system to eliminate cancer cells. This class of drug is used

in conjunction with chemotherapy and is chosen based on a variety of factors, including the stage of cancer. New findings, like immunotherapy, are beginning to dispel the myth that triplenegative breast cancer is incurable. Mammograms should begin at the age of 40, according to experts. The frequency and timing of screenings are determined by your specific risk, therefore it's critical to consult with a health care provider to evaluate your risk and when to start screenings. Meanwhile, everyone should be mindful of any changes in their breast symptoms. It's also crucial to be conscious of one's body and to detect any changes, reporting them to a doctor if necessary. Finally, specialists advise that knowing your family history is critical because it may influence your risk of breast cancer. To conclude, it can be said that triplenegative breast cancer is becoming more curable as additional discoveries are revealed offering doctors and patients living with the disease hope.

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