# The Growth and Spread of Breast Cancer: A Comprehensive Review

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## Introduction

Breast cancer is the second leading cause of cancer-related deaths for females, behind lung cancer [2]. Breast cancer is fueled by the hormone, estrogen, that binds to the estrogen receptors and regulates important processes related to reproductive health. There are many different subtypes of breast cancer that can be a predictor of how it responds to treatments such as hormone therapy and chemotherapy [3]. The triple-negative subtype, which does not have receptors to estrogen, progesterone, or the HER2 gene, will require a stronger treatment such as chemotherapy, while other subtypes with distinct combinations of positive and negative receptors to estrogen, progesterone, and HER2 can be treated effectively with hormone therapy or other, less aggressive alternatives [Figure 1]. The purpose of understanding the factors involved in the spread of breast cancer is to discover less invasive treatment methods that do not impact a patient's quality of life, and can help lower the rate of breast cancer deaths.

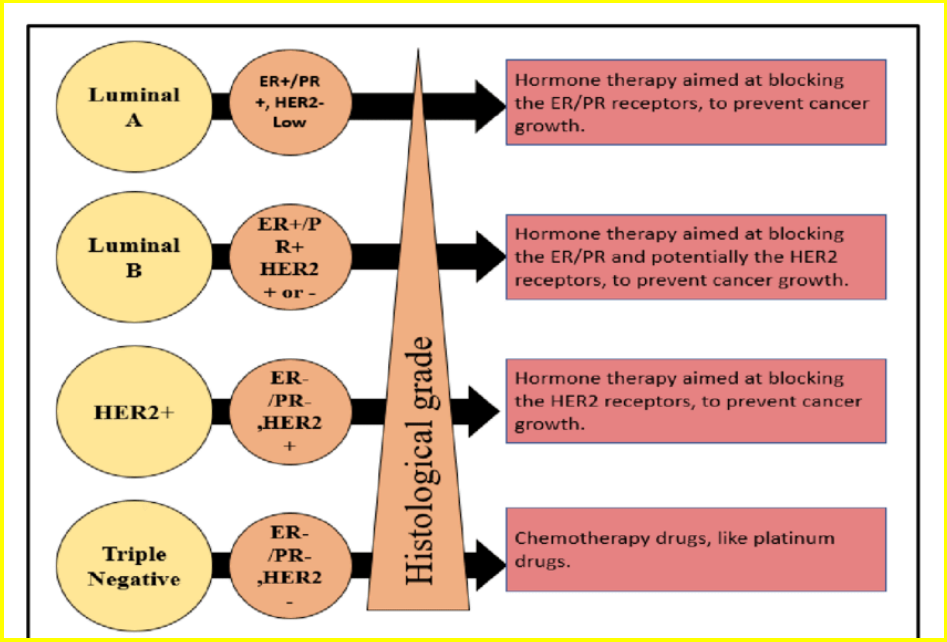


**Figure 1**. Breast cancer subtypes and the effective treatments for their hormone and gene receptor levels [4].

## Cell Cycle and DNA Replication

An organism's survival depends on its ability to replicate genomic DNA. In order to replicate DNA, a cell must first go through the stages of the cell cycle. The cell cycle is the process by which cells divide. In the first stage, G1, the cell copies organelles, and expands to prepare for S phase [3]. Next, is the S stage, where the cell replicates the DNA to have one copy for each cell. In G2, the cell continues growing to ensure that the cell is completely ready for Mitosis [3]. The cell spends 90% of its time in the first 3 stages while preparing for Mitosis [2]. While the cell cycle's main purpose is to create copies of cells, an important factor before this can happen is DNA replication.

DNA replication begins with single-stranded binding proteins and helicase binds to the DNA at multiple origins, which aid in separating the strands to create the replication bubble [5]. Origin-binding proteins are used to keep the origin open so that helicases can unwind the strands completely [5].

Multiprotein complexes perform the replication, beginning with a primase which places RNA primers on the leading and lagging strands to act as a template for the polymerases that go through each strand separately [Figure 2]. On the leading strand, DNA polymerase runs in the 5' to 3' direction, and replaces the RNA primers with the respective nucleotides needed to complete the double helix [5]. On the lagging strand, DNA polymerase adds nucleotides 5' to 3' starting at the 3' end of the lagging strand. Due to the replication leading away from the replication origin, it generates fragmented DNA, termed Okazaki fragments. The Okazaki fragments are later filled in by a ligase to create a continuous strand. Once both double helixes are completely copied and separated, the cell enters G2 and progresses into Mitosis [5].

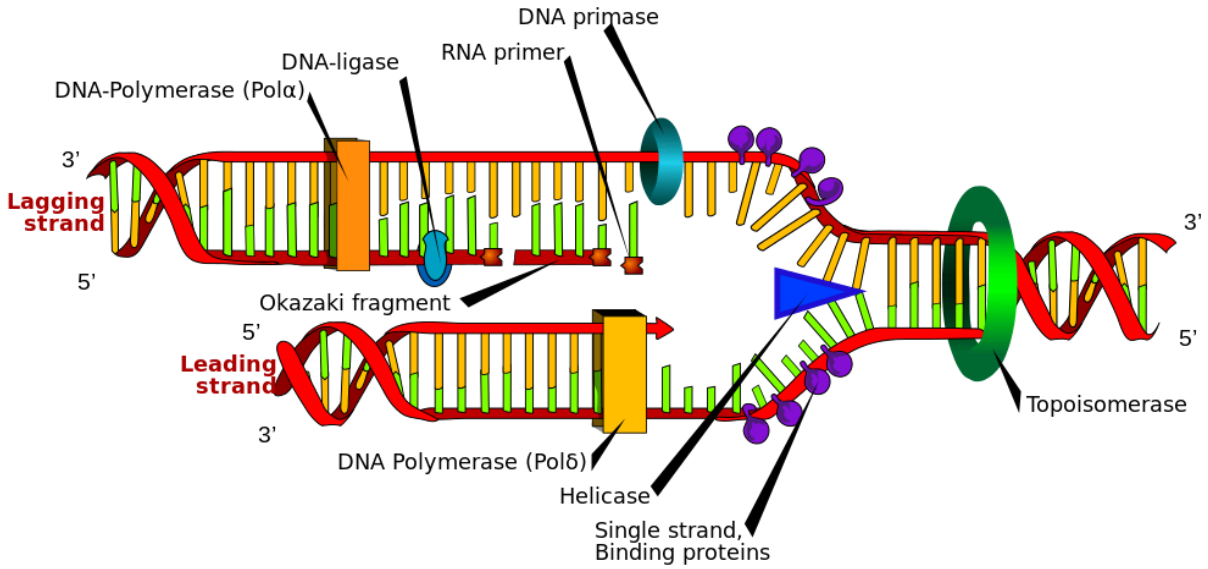


**Figure 2.** DNA replication with the proteins involved in the process [6].

If the cell has passed through the checkpoints, it will begin mitosis. The first phase of mitosis is Prophase, where chromatin is condensed into chromatid strands, the nuclear envelope disperses as nucleoplasm into the cytoplasm, and spindle microtubules begin to form [7]. Next, in Prometaphase, kinetochores form on the chromatins for the spindle to attach to. The spindles align the chromosomes at the spindle equator where they are lined up to form the metaphase plate. Anaphase begins when sister chromatids separate as the spindle retract. The spindle poles are distanced from each other as the cell elongates, and the chromatids are pulled to opposite ends. Following the separation of the chromatids, telophase begins, and a nuclear envelope begins to reform around each set of chromosomes and spindle poles. In the final phase of mitosis, cytokinesis, the cytoplasm and the cell membrane separate to form 2 daughter cells [7].

**DNA Repair Pathway Failures and Mutation Accumulations**

There are many different factors that can lead to cancer, including genetic and external factors. Some genetic factors include failures in cell cycle checkpoints, DNA mutations, and issues with DNA repair pathways. The cell cycle has three checkpoints which occur after G1, before M phase, and during M phase [Figure 3]. The purpose of the first checkpoint after G1 is to ensure the cell is large enough and has the proper proteins to successfully complete DNA replication, as well as checking for DNA damage [2]. In the next checkpoint after G2, the cell ensures that all the DNA has been duplicated properly and is not damaged. The final checkpoint in the cell cycle occurs during the metaphase stage of Mitosis where the cell checks that all the spindle fibers are properly attached to the sister chromatids before separating. If any chromosomes are not attached to a spindle fiber, the cell will pause mitosis until the chromosomes

are all properly aligned [2]. The cell would not continue with the cell cycle if it encountered an issue at a checkpoint such as DNA damage or mutations [6].

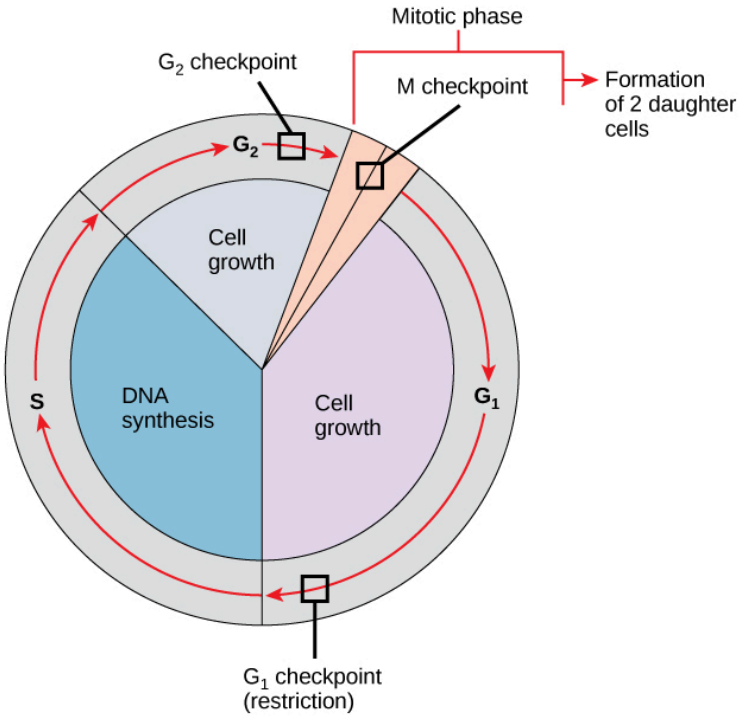


**Figure 3.** The phases of the cell cycle with their respective checkpoints [3].

Despite having checkpoints to prevent damage, endogenous and exogenous factors can be mutagens by causing direct or indirect DNA damage [8]. Such mutagens are either chemical or physical factors that can be naturally occurring or from external factors [8]. Exogenous examples are damage arising from UV radiation, tobacco, chemicals, and radioactive substances, to name a few [9]. Meanwhile, examples of endogenous factors would be replication errors, and reactive oxygen species [10]. These factors can lead to single-stranded DNA mutations or breaks (ssDNA) or double stranded breaks (DSBs), which cause an accumulation of mutations if not properly repaired [9].

While there are different types of DNA damage, certain factors can lead to one type of damage over the other. Replication errors can lead to mismatches because the wrong nucleotide was synthesized into the daughter strand that does not match the original complementary nucleotide or no base is added at all, leading to a ssDNA break [8]. If it is not fixed, the mutation will be permanently sustained in the next round of replication because it can lead to a double strand break [8]. Mutations that are not point mutations may happen when DNA reacts with a mutagen, which changes the structure of the strand, such as the use of chemotherapeutics, which can often cause crosslinking [11]. Reactive oxygen species,such as hydroxyl radicals (OH), can be stimulated by pollutants and radiation, and cause bases to oxidate and become damaged [12]. These different types of damage can be repaired using different processes [Figure 4].

Two of the most common DNA repair pathways are base excision repair (BER) and Homologous recombination (HR) [12]. The BER pathway is made up of two sub-pathways that deal with base damage, short-patch BER and long-patch BER, which replaces a single nucleotide or multiple nucleotides, respectively. Both sub-pathways start by removing the damaged base, forming a gap in the strand and then filling it in with the proper nucleotides. The purpose of the HR pathway is to repair DSBs

to prevent mutations. Many proteins locate and repair broken pieces of a strand by copying undamaged pieces in HR [12]. DNA damage can accumulate and lead to cancer if the repair pathways fail or are overwhelmed.

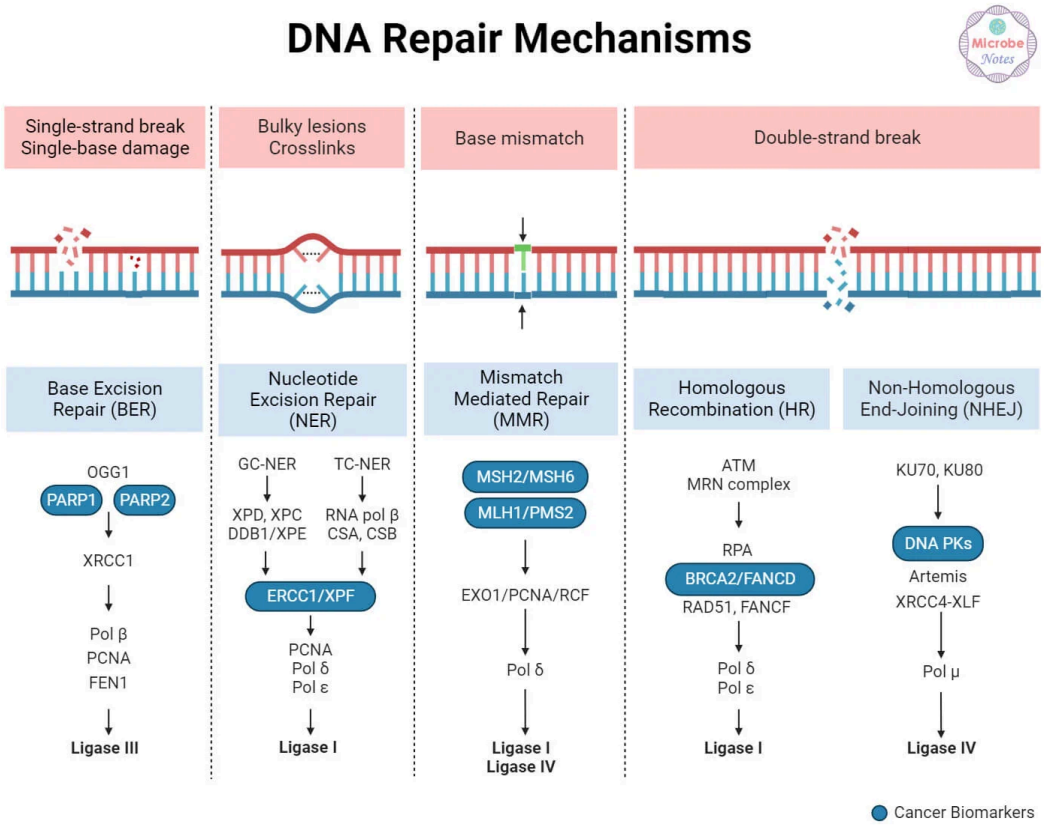


**Figure 4.** Pathways and mechanisms used to fix different kinds of DNA damage [13].

Issues in these repair pathways can arise from mutations in certain genes that are important in the success of the DNA damage repair. For example, mutations in an activator of the BER pathway, TP53, are among the most frequent in cancer diagnoses [14]. BRCA1 and BRCA2 are genes used to activate the HR pathway, and they can be inactivated by inherited mutations [13]. Possessing mutations in these genes can pose a greater risk of getting cancer [13]. If the repair pathways fail due to mutations of certain genes, the cell growth may progress until it metastasizes into other parts of the body.

**Metastasis of Breast Cancer**

Metastasis of breast cancer begins after the primary tumor has spread from the connective tissue to the lymph nodes, and begins to form a secondary tumor [15]. Some cells detach themselves from the extracellular membrane (ECM) and begin to migrate [16]. The cells attach themselves to the walls of blood vessels and travel through the bloodstream to different parts of the body. The cells circulate to other organs, and undergo cell-cycle arrest to stick to the walls of the organs they invade. Once they reach the desired location, they begin to multiply and form secondary metastases [16]. The four most common sites of cancer metastasis are the brain, liver, lungs, and bones. With nearly 30% of women diagnosed with early-stage breast cancer developing into metastatic breast cancer, we are in need of more effective treatments [17].

**Common Treatments of Breast Cancer**

Although treatments differ based on tumor stage and pathology, common treatments for breast cancer include local surgery or radiation, and systemic chemotherapy, hormone therapy, immunotherapy, and targeted drug therapy [18]. Surgery can be done both proactively or retroactively. Women who have done genetic testing and know they have mutations that predispose them to getting breast cancer may have a mastectomy done, as well as women who have stage 1 or 2 breast cancer. Radiation is used to destroy early-stage cancer cells before they can spread. Chemotherapy, which is the systemic administration of drugs to kill cancer cells, can be used throughout the treatment process, and is administered via an IV or oral pill. Hormone therapy typically lowers estrogen and progesterone levels to prevent fueling the growth of breast cancer, and can be administered as an injection or an oral pill. Immunotherapy uses medicine to strengthen the immune system so that it can destroy cancer cells more efficiently, and is administered via IV. Targeted drug therapy slows the spread of cancer by using medicine directed towards destroying proteins on cancer cells that help them grow and spread faster. These medicines can be taken as pills or injections. Different treatments can be used depending on the stage of cancer growth and the resources available in the different parts of the world [18].

**Distribution of Cancer**

Breast cancer diagnosis and survival is partly dependent on where someone resides in the world. Different carcinogens such as pollution, alcohol consumption, and chemicals from certain products, may affect individuals more in some locations rather than others–depending on their amounts. Access to treatments as well as early diagnosis depends on the amount of resources in each country. For women in the United States, a country with relatively accessible breast cancer screening and treatment opportunities, the rate of surviving after five years with metastatic breast cancer from 2012 to 2018 was 90.6%, and the mortality rate in 2015 was 13.3/100,000 cases [23]. Similarly, a study including 27 European countries, many offering universal healthcare, reported that on average, breast cancer related mortality had dropped from 15/100,000 to 14.4/100,000 cases from 2012 to 2017 [23]. These two facts demonstrate how developed countries with accessible preventative screening and treatments for breast cancer have had declining or reduced mortality rates as our technology and understanding of breast cancer improves. Conversely, Argentina and Uruguay had mortality rates of 24/100,000 in 2008, the highest of Latin America that year [23]. Other Latin American countries had mortality rates closer to that of Europe in the same year, however, total breast cancer related deaths in Latin America are expected to reach 92,700 by 2040; negative economic development and unhealthy lifestyle changes–such as obesity and alcohol consumption–are likely factors attributing to the expected increase of total deaths [23]. Likewise, breast cancer mortality rates increased by 13% from 1990 to 2017 in Sub-Saharan Africa, possibly due to a low screening rate of 12.9%, resulting in many diagnoses of late stage breast cancer [23]. Comparably, the mortality rate in South Asia is expected to increase by 35% from 13.4/100,000 to 18.1/100,000 cases by 2030, and in East Asia it is expected to increase by 7% from 9.1/100,000 to 9.88,100,000 cases [23]. In China, mortality rates from 1997 to 2009 increased by 20% in rural areas, and decreased by 7% in urban areas due to increased awareness and preventative measures in urban areas, and low accessibility for preventative care and treatment in rural areas [23]. These statistics about Latin America, Africa, and Asia all display the significance of a healthy lifestyle, access to resources, and awareness about breast cancer when treating breast cancer and seeking to decrease mortality rates globally. Early screening opportunities and access to effective treatments are essential so that women with breast cancer may be diagnosed and treated in earlier stages in order to provide a higher possibility of survival.

**Conclusion**

In the United States, 1 in 8 women will be diagnosed with breast cancer and will have a 10-year relative survival rate of 84% [17]. While lifestyle choices may influence the likelihood of developing breast cancer, most cases are linked to genetic predispositions or gene mutations. During the cell cycle, a cell will go through growth and DNA replication, where many errors can accumulate, leading to cancer

if not properly fixed by DNA repair pathways. Early diagnosis will increase an individual's probability of success in responding to treatment such as surgery, radiation, and chemotherapy, among others. In the event that these treatments fail to stop the spread of the cancer cells, it may metastasize through the bloodstream and eventually infect other organs, such as the lungs, liver, and brain. This underscores the importance of understanding why breast cancer forms and continuing to research more effective ways to treat and prevent a breast cancer diagnosis, ultimately reducing the global burden of this disease.

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