

# Breast Cancer; Updated and deep insights.

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## **Abstract:**

Breast cancer is the most common cancer to be diagnosed in females throughout the entire world, and it is also the primary reason why people lose their lives due to malignant tumours. The risk of developing breast cancer is increasing at an alarming rate over the whole planet. In light of this, it is essential to search for innovative therapeutic techniques in addition to predictive and prognostic indicators, notwithstanding the progress that has been made in identifying and treating the disease, which has resulted in a reduction in the overall mortality rate. Several distinct therapy modalities are utilised, each of which is determined by the molecular subtype. Systemic therapy and locoregional therapy, which include surgery and radiation therapy, are both components of the multidisciplinary strategy that is taken to treat breast cancer. Chemotherapy, anti-HER2 therapy for diseases that are positive for HER2, hormone therapy for diseases that are positive for hormones, and immunotherapy, which was developed more recently, are all examples of systemic therapies. Triple negative breast cancer accounts for between 15% and 20% of all breast cancers. This subtype of breast cancer affects more than 15% of patients. As a result of its poor response to treatment and the exceedingly invasive nature of the condition, it presents a therapeutic challenge and, as a result, generates a significant amount of research interest. The treatment of breast cancer in the future will hopefully be more individualised, with the ability to de-escalate when necessary and escalate when necessary based on the biology of the tumour as well as an early therapeutic response. This article provides an overview of the research that has been done on breast carcinoma, which is a disorder that affects women all around the world.

## **1. INTRODUCTION**

The term "cancer" comes from the field of medicine and refers to the uncontrolled multiplication of cells that occurs when this process is allowed to go without being stopped[1, 2]. Tobacco use,

exposure to toxins and ionizing radiation, viral infections, some other components of nature, genetic diversity, thyroid hormone, being in an immune-compromised posture, and arbitrary change are some of the potential triggers that might lead to the development of cancer[3, 4]. A large variety of additional factors, such as certain diseases, a lack of physical activity, being overweight, and exposure to toxic metals, can also increase the likelihood of getting cancer[5]. The DNA or RNA found in tumor cells is genetically identical to that found in the cells of the organism from whence the tumor cells originated. Because of this, inflammatory reactions often are unable to detect them, particularly if they are of a low intensity[5, 6]. This is especially the case if the person in question is frail. As a result of differences in their DNA and RNA, healthy cells have the potential to give rise to cancerous tumor cells[7]. On the other hand, apart from temperature, toxins found in the atmosphere, moisture, or nourishment, electrical cell damage, oxidative stress, speciation, or ageing of DNA or RNA, all of these components that can cause the improvements of genetic changes, include pivotal emission, cosmic emission, pathogens, microbes, as well as yeasts, protozoa, and a wide variety of other components. Every single one of them has the potential to bring about different manifestations of the condition[8]. Because it was discovered that cancer is linked to an increase in the unpredictability of the organism to the point where the body is unable to self-correct, this condition became known as a "entropic disease." It is necessary to have assistance from the outside environment in order to bring the organism back to an entropic condition that is stable[9, 10]. On the other hand, the organism will finally perish if the process of defense is not carried out effectively and an excessive number of cells are created[11]. As a consequence of this, there is a possibility that cancer will grow if inflammatory reactions seek to get rid of anything[12]. The frequency of DNA or RNA genetic variations can be excessive only under certain conditions, such as an unpleasant environment (due to exposure, toxins, or other factors), poor foodstuffs (which lead to an undesirable cell habitat), individuals who have a genetic predisposition for mutations, and elderly people, according to research published in *Advances in Molecular and Cellular Biology*[13].

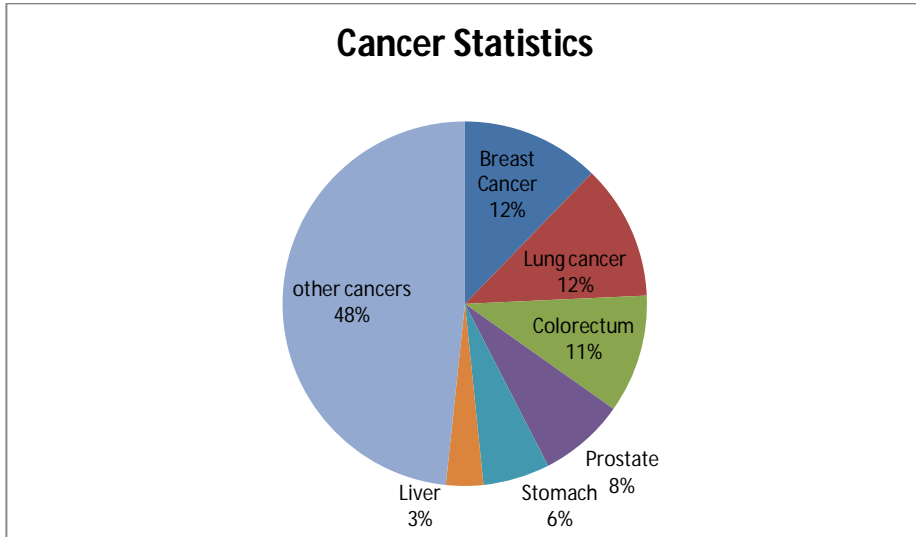


Figure 1 cancer statistics [14]

#### 1.1 Classification of cancer:

Histopathology sorts, which relate to the different kinds of tissue in which they develop, and initial locations, which refer to the sections of the body where they originally emerged are the two categories that are used to classify cancer. There are many different kinds of cancer[15]. The most prevalent kind of cancer is referred to as a histopathology sort. Cancers originating in the initial areas are the second most prevalent form. Regarding the designation and histological classification of such conditions, the worldwide classification of oncology illnesses, fourth volume, continues to represent the consensus view among medical professionals all over the world (ICD-O-3). The majority of malignancies may be placed into one of six primary groups, according to a number of studies on histology[16-19].

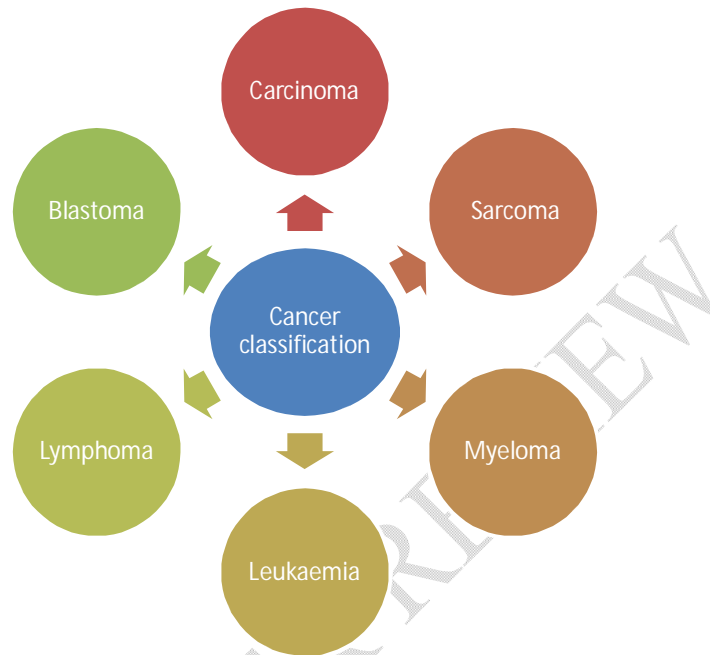


Fig .2 Classification of cancer

## 2. Breast cancer

The unregulated maturation or proliferation of the cells that form inside of the breast can lead to a condition known as breast disease. According to the findings of Applic et al. (2004), malignancy is typically named for the anatomical location in which it arose. Cancer of the breast is a word that is used to describe the condition that occurs when breast cells in the breast develop outside of their normal parameters. There are several different risk factors that might lead to breast cancer. The type of breast cancer that a patient has will be determined by the types of cells that were damaged by the tumour. It is possible for this cancer to grow in any part of the breast. It would appear that the three most important structural components of the breasts are the lobules, the ducts, and the soft tissue. The lobules are responsible for the production of milk, which is then carried to the nipple through the ducts. Connective tissue either encases everything or binds everything together in some way. Cancer of the breast almost always begins in the

lobules and spreads via the ducts. According to Advances in Cancer Research (2010), arteries make it possible for cancer to spread to other organs.

Cancer of the breast has a complicated phenotype: carcinoma in situ and invasive carcinoma may coexist, as mixed histological kinds of invasive carcinoma, and infiltrating ductal carcinomas frequently comprise regions with varying degrees of disease severity. This morphological heterogeneity matches the molecular heterogeneity that is present, as well as the fact that morphologically comparable tumours may differ in their genetic and metabolic processes, and that specific genetic defects may impact clinical prognosis [20-22].

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With an elevated incidence of 14.1 million new cases in the year 2012 and a high mortality rate of around 8.2 million fatalities all over the world, breast cancer is the most often diagnosed form of cancer in females. It is anticipated that the incidence rate would rise by the year 2020, reaching a level that is almost twice as high as the rate in 2012. It is anticipated that young women between the ages of 20 and 59 will be diagnosed with breast cancer, and there will be an increased risk of mortality from cancer within this age group [23-25].

### 2.1. Etiology:

It is a multistep process that turns normal epithelium into cancer. cancer begins as normal epithelium. Breast cancer can be caused by a combination of variables, including those in the food, the environment, and one's genetic heritage. Because there is a healthy equilibrium between negative and positive growth factors in normal breast tissue, the development of breast cancer requires either a reduction or an increase in certain functions. The development of breast cancer may be influenced by a number of variables, including those listed below:

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**Comment [MF3]:** one's genetic heritage and epigenetic modifications.

- Age

**Comment [MF4]:** Reference?

It's possible that the accumulation of somatic mutations is to blame for the rising rates of breast cancer seen with advancing age. Both beginning menstruation at a younger age and delaying menopause until later in life lengthen the period of time a woman is exposed to ovarian hormones, which has been linked to a higher risk of breast cancer. There is some evidence to suggest that breast cancer in younger women is more aggressive than breast cancer in older women. This would be consistent with a more quickly growing disease that declares itself clinically earlier.

- **Factors Related to Genetics**

It is believed that complex acquired genetic modifications are the cause of breast cancer, and it is likely that genetic anomalies in the premalignant and malignant breast epithelium play a role in the development of the disease. The fact that only five percent of breast cancer patients have a significant family history that points to the inheritance of mutations that promote tumour growth in the germ line provides compelling evidence that the majority of breast cancers are caused by acquired mutations. BRCA1 and BRCA2 are two genes that are substantially responsible for the inheritance of breast cancer in its early stages. Other conditions that are linked to an increased risk of breast cancer include the Li-Fraumeni syndrome, ataxia telangiectasia, and Cowden's disease.

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- **Hormonal status**

Exposure to mammotropic hormones, including oestrogen, progesterone, prolactin, and insulin-like growth factor 1 during adolescent and adult life tends to increase the chance of developing breast cancer. It is possible that this might be explained by an increased epithelial cell population that is vulnerable during the preinitiation stage, which affects clonal expansion and modulates growth augmentation in subclinical tumours. Although oestrogen is the primary factor in breast development, the role it plays is contingent on the presence of oestrogen receptor (ER) expression in the target tissues. Over the past few years, it has come to light that women who have an overexpression of oestrogen receptors in their normal breast epithelium have an increased risk of developing breast cancer.

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- **A history of noncancerous breast illness**

There is abundant evidence indicating that several subtypes of benign breast disease are linked to the development of breast cancer. In benign breast neoplasia, the inactivation of tumour suppressor genes and loss of heterozygosity have both been documented as potential outcomes. Although ductal and lobular carcinomas in situ do not have the ability to invade or metastasize, they do have a partly malignant morphological phenotype and are associated with an increased risk of invasive cancer. Other lesions that are associated with abnormal cell proliferation are also associated with a slightly increased risk of developing cancer. These lesions include atypical hyperplasia (both ductal and lobular), florid hyperplasia of the usual type (that is, without atypia), and florid hyperplasia without atypia. Although the frequent coexistence of premalignant lesions and invasive breast cancer is consistent with progression from these lesions to cancer,

there are many controversies in this area, and clonal relationships are not always clear [4]. However, progression from these lesions to cancer is consistent with progression from these lesions to cancer.

### **2.1.1. Omics” and promising biomarkers in breast cancer**

Recently, with the merging of “omic” technologies such as genomics, proteomics, metabolomics, transcriptomics, etc., a great advancement has been achieved in the field of cancer biology with better understanding of carcinogenesis, cancer progression, metastasis, and target therapy. Microarray, mass spectrometry, and sequencing techniques provide evolutionary era for promising cancer biomarkers . Transcriptional profiling has been reported as a valuable tool for classification and determination of prognosis in patients of breast cancer. Apart from diagnosis, prediction of response to therapy, and prediction of breast cancer patients’ outcomes, biomarkers may estimate risk assessment of getting cancer. Genetic alterations in breast cancer or methylation of promoters of cancer-specific or associated genes will definitely linked to altered expression of certain proteins and may be used as emerging cancer biomarkers [26].

### **2.2. Epidemiology:**

The most frequent malignant tumor in women worldwide is breast cancer. Up to 36% of oncological patients are breast cancer patients. In 2018, an estimated 2.089 million women received a breast cancer diagnosis [27]. All across the world, the prevalence of this cancerous tumor is rising, but it is more prevalent in developed nations. A global average shows that industrialized nations account for about half of the instances. This tendency is mostly attributable to the so-called Western lifestyle, which is known for its unhealthy eating habits, nihilism, high levels of stress, and lack of exercise. Mammography is now accepted as a screening method for breast cancer. Women between the ages of 50 and 69 are the group of women who benefit from mammography the most. Classical mammography has a sensitivity range of 75–95% and a specificity range of 80–95% [28, 29]. Magnetic resonance mammography is utilized as a screening test for women who may have hereditary breast cancer. If a worrisome lesion is discovered during a mammogram, a thick needle biopsy may be required, coupled with a histological evaluation of the tumor [30, 31].

In 2018, there were 66,101 instances of breast cancer in Japan, 55,439 cases in the United Kingdom, 56,162 cases in France, 71,888 cases in Germany, and 85,5/105 cases in the United States (all crude rates of 85/105) [32, 33]. Belgium has the greatest crude incidence rate in the

globe (113/105), and Australia has the highest crude incidence rate among the continents (94/105) [33]. Breast cancer is the most often diagnosed malignant tumor among women in Poland. The number of instances has steadily increased (1990 saw 8000 new cases; 2018 had 20,203 new cases). In Europe, the incidence rate is 84/105 on average. The nations of Southeast Asia and Africa have the lowest incidence rates, with a standardized incidence rate of no more than 25/105 [33]. The Republic of The Gambia (crude rate: 6.5/105) and Bhutan (crude rate: 5/105) had the lowest incidence rates in 2018[33].

Breast cancer is the leading cause of mortality from malignant tumours in women worldwide, despite improved early diagnosis or the quick development of pharmacotherapy in recent years. 626,679 people lost their lives to breast cancer in 2018. Contrary to morbidity, the highest rates of mortality from this malignant tumour are found in developing nations, where up to 60% of all breast cancer deaths occur (Fiji, crude rate 36/105, highest rate; Somalia, crude rate 29/105; Ethiopia, crude rate 23/105; Egypt, crude rate 21/105; Indonesia, crude rate 17/105; Papua New Guinea, crude rate 25/105) [34].

This tendency is mostly due to the lower screening rates than in wealthy nations, the accessibility of diagnostics, and contemporary treatment approaches. In comparison, the standardized death crude rate was 16.3/105 in Belgium, 13./105 in the US, and 9.3/105 in Japan. Poland has a substantially lower incidence of breast cancer than other EU nations (the standardized incidence rate for Polish was 51.8 in 2013 compared to 106.6 for the EU). Over the past 30 years, the prevalence of adult premenopausal women (20-49 years old) has nearly doubled [35]. Unfortunately, Polish women still don't seem to care all that much about prevention. They disregard the health of their breasts and downplay the value of routine checkups. Polish women receive less preventative treatment than women in other European nations; in the Netherlands, 80% of women claim access to free mammography prevention program, in England, 71%, and in Poland, just 44%. The 5-year breast cancer survival rate in Poland is 78.5%, which is much lower than, for instance, the 90% figure obtained in the United States[35-38].

### **2.3. Classifications of breast cancer**

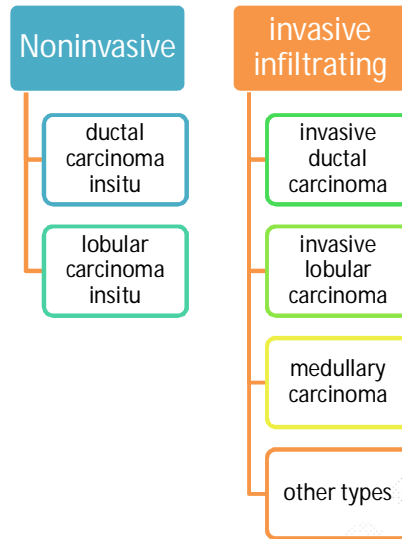


Figure 3 Who classification of breast cancer [39]

- Non-invasive breast cancer

Intraductal adenocarcinoma is also referred to as DCIS, which stands for ductal carcinoma in situ. This type of breast cancer, which is non-invasive and pre-invasive, is ductal carcinoma in situ and is one of the most common types of breast cancer[40, 41]. It comes out from within a duct that is already present in a typical environment. Even though ductal carcinoma in situ (DCIS) does not spread to other parts of the body on its own, it has an extremely high risk of progressing into invasive tumours. Therefore, in order to protect any individual from developing invasive cancer, early diagnosis and the appropriate treatment are required[42, 43].

### 2.3.1. Infiltrating breast tumors

These are invasive and spread to the breast stroma that is adjacent to them. Additionally, they penetrate beyond the lobules and ducts that are typically found in the breast. They are found, and almost two-thirds more women diagnosed with an aggressive form of cancer are 55 years old or older. Invasive malignancies always have the potential to spread to other parts of the body, including organs and lymph nodes, and have the ability to move throughout the body. As a result, tumours of the breast that are particularly aggressive fall into this group. Depending on the kind of cells or tissues involved in the process[44, 45]. There are many subtypes of invasive breast cancer, however they may be broken down into two categories:

- **Invasive ductal carcinoma (IDC)**, which is the most common. IDC, or invasive ductal carcinoma, is by far the most common form of breast cancer. It is estimated that around 80 percent of all breast cancer cases are caused by IDC. Some of the subgroups that are included in the IDC category are breast cribriform carcinoma, breast capillary cancer, breast mucinous carcinoma, and breast tubular carcinoma. Other subgroups include breast medullary carcinoma and breast tubular carcinoma[46-48].

- Invasive lobular carcinomas (ILC):

Invasive lobular carcinoma (ILC), the second most common kind of tumour, accounts for around ten to fifteen percent of all cases of breast cancer. Although it can affect women of any age, ILC is most commonly seen in women who are middle-aged or older. The ILC subtype accounts for about 90–95 percent of all breast cancer cases. Malignancies of the IDC and ILC have distinct diagnostic features that are present[49-51]. Lobe carcinomas, on the other hand, arise from live cells that are arranged singularly, as single files, and in sheets. This is in contrast to duct carcinomas. In addition to this, they have a number of molecular and genetic abnormalities. It is of the utmost importance to differentiate between ductal and lobular carcinomas since the prognoses and treatment options for each kind of carcinoma can be quite distinct from one another. Metastatic breast cancer, papillary carcinoma, phyllodes tumors, and breast angiosarcoma are some of the less common subtypes of breast cancer. There are many other, less common types of breast cancer. Different patients diagnosed with breast cancer exhibit a variety of symptoms. There are many people who do not exhibit any symptoms at all[52, 53].

#### **2.4. Triple Negative Breast Cancer:**

Triple-negative breast tumors, or TNBCs for short, are among the most aggressive types of breast cancer. These cancers develop as a result of aberrant progesterone, estrogen, and human growth factor receptor 2 expression in the breast tissue[54]. According to immunohistochemical results, TNBCs frequently exhibit cellular expression of progesterone and estrogen receptors of 1% and human growth factor receptor 2 expressions between 0 and 1+ [55]. The American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) created these recommendations. TNBCs may be classified into four different transcriptional subgroups. Among these are the two basal subtypes BL1 and BL2, the mesenchymal subtype M, the luminal

androgen receptor subtype, and the androgen receptor-positive subtype of TNBCs. Additionally, TNBC may be categorized into six different subgroups based on the molecular heterogeneity of the tumour: immunomodulatory, luminal androgen receptor expression, mesenchymal stem-like, mesenchymal-like, basal-like, and unstable. Subtypes are created by further segmenting these subgroups. TNBCs account for 12–17% of all breast cancer cases and have a history of spontaneous recurrence[56]. This form of breast cancer is categorised as a less frequent subgroup within the more broad category of breast cancers. TNBCs exhibit more aggressive behaviour when compared to the clinical characteristics of other breast cancer subtypes. These tumours have a poor prognosis, and are distinguished by specific patterns of metastasis. Triple-negative breast cancers (TNBCs), which make up 24 percent of newly diagnosed instances of breast cancer, have been increasing in frequency. TNBC was the most common kind of breast cancer in women in 2018, with an estimated 2,088,849 cases detected, according to Singh et al.'s research from 2020[57]. In light of the medication that is currently available, the average survival rate from the disease is approximately 10.2 months, with a 65% 5-year survival rate in cases with regional tumours and an 11% survival rate in cases where the tumour has spread to distant organs [58].

## **2.5. Breast cancer stages**

The stage of the disease is determined by both the extent to which cancerous cells have spread throughout the breast tissue as well as the type of cells that have been affected. In comparison, stage 0 included the infiltrating type of non-invasive cancer and described stage 4[44, 59]. The following is a description of the many stages of cancer:

### **2.5.1. Stage 0**

DCIS, or ductal cell carcinoma in situ, is a good example of such a disease stage since it reveals that both malignant and non-malignant cells have been contained inside the boundaries of either the region of a breast where the cancer cells first emerge. This stage of the illness occurs when the cancer cells are still in the early stages of their development. In one research it is stated that they are not preserved as proof of invasion in the tissues around the entire region[60, 61].

### **2.5.2. Stage 1**

Because there is still the possibility of a microscopic invasion, each stage can be thought of as a form of cancer that spreads by infiltrating healthy tissue. There are two variations of this step: step 1A and step 1B. step 1A refers to cancers that are longer than in length and are not associated with any lymphatic system, whereas step 1B refers to a small cluster of tumour tissue that is larger than 0.2 millimetres and is found in a lymph system. Both of these stages are considered malignancies[62, 63].

#### **2.5.3. Stage2**

In addition, there are two variations of this phase, designated 2A and 2B respectively. Cancer that has been found in the lymphatic and circulatory systems but not in the chest cavity is depicted in Phase 2A of the staging process. This cancer might be as little as less than 2 centimetres or as large as over 5 centimetres in size. On the other hand, phase 2B indicates that the cancer may be larger than 5 centimetres in size but that it has not migrated to the axillary lymphatic nodes [64].

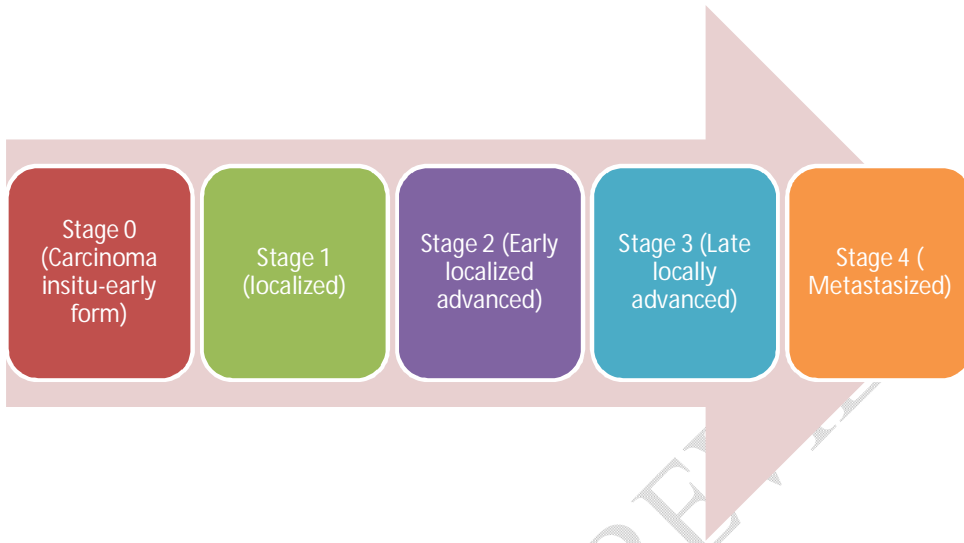
#### **2.5.4. Stage3**

This level is broken up into three distinct divisions, numbered 3A, 3B, and 3C respectively. Step 3B explains every length of cancer that was caused by inflammation and an ulcer upon this breast's skin and has expanded to as many as nine axillary lymphatic nodes or just to sentry lymph nodes, whereas step 3A explains cancerous cells that have not been discovered inside the chest, and they may be discovered in four to nine axillary lymphatic nodes or within guardian lymph nodes. In point of fact, phase 3B tumours can be classified as inflammatory due to the fact that the surface of the tumour is reddened, heated, and puffed up. Therefore, the expansion of the malignancy to 10 is included in phase 3C of the process. According to Jacquillat C.'s research from 1989, the lymph nodes that make up the lymphatic system may be found behind the collarbone and in the axilla[65, 66].

#### **2.5.5. Stage4**

The proceeding or progression stage of the illness refers to the spread of the disease to further organ systems, such as the liver, the brain, the lungs, the bones, and so on [67, 68].

Fig.4 Breast cancer stages



### 3. Breast Cancer history:

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In contrast to a group of women who did not have any disorders, those who have had chest cancer in the past are more likely to get it one or more times in their lives. The presence of either malignant or non-malignant breast tumours is associated with an increased risk of developing tumours in the future[69].

### 3.1. Hard Chest cells

- Mammary cells with a larger thickness are associated with an increased likelihood of developing chest cancer. It appears that persistent hormonal shifts may increase the risk of developing a chest tumor. This must be the outcome of the menstrual cycle starting earlier than usual, in conjunction with anovulation starting later than usual. During this time period, hormone levels tend to be higher. Suckling, particularly after the age of one year, appears to reduce the risk of developing a chest tumor. This is likely because both pregnancy and lactation reduce the amount of hormones consumed by the body[70].

### 3.2. Construct the mass

- Consuming an excessive amount of fructose might be a factor. Because higher hormone levels are present during menstruation, it is possible that women who are obese and have a round figure have a higher risk of developing breast cancer[71, 72].

### 3.3. A person who drinks beer:

- It appears that this is connected to a loosening of restrictions on drinking heavily and frequently. Emission display the medication of the tumor that does not carcinoma raises chances of developing a check tumor behind under viability. This is due to the fact that drinking more than three beers on a regular basis is associated with a one and a half times greater risk of developing breast cancer in women[73].

### 3.4. Estrogen medicine

- Employment for **oestrogen** substitution treatment, also known as (hormone replacement therapy), with oral pregnancy prevention pills was previously connected with cancer. This association was made because to the higher hormonal alterations that were caused by the treatment[74].

### 3.5. Diethylstilbestrol's manifesting characteristics

Comment [MF8]: estrogen

- **Diethylstilbestrol** manifestation was another hormone-like drug that women who were pregnant took beginning in the 1940s and continuing until the middle of the 1970s. They did this in the belief that it would lower their chances of having a stillbirth or abort their unborn children. Cancer strikes young women at a somewhat higher rate than it does older women. Women who gave birth while using diethylstilbestrol had a considerably elevated risk of getting chest cancer between the years 1949 and the mid-1970s [75].

Comment [MF9]: correct

### **Diagnosis:**

Mammograms and ultrasounds were among the early types of scanners. Individuals who are experiencing tissue growth or repair, particularly along the course of a chronic disease, those who actually appraise for bilateral illness, and those who are concerned about the significant likelihood of developing chest tumour cancer are all candidates for MRI evaluation[76]. Individuals with thick chests, bilateral illness, and a history of chest chemotherapy and radiotherapy could be evaluated using magnetic resonance imaging, which could further storage and help arrange perioperative medication for histopathology tumours[77].

Comment [MF10]: add molecular analysis of specific genes related with BC as diagnostic method

UNDER PEER REVIEW

- MRI allows for a more accurate diagnosis of epidermis changes that are characteristic of infiltrative tumours, such as epidermal infiltration. The randomly orientated tumour, architectural misalignment, armpit lymphadenitis, and echogenic darkening are all broadly diagnostic signs for aggressive, invasive tumours. Additionally, occasionally ductal micro calcification precipitates can be seen [78].
- The presence of cancer may be determined through the use of cell biopsies; specimens were acquired by the use of endoscopic ultrasonic central injection biopsies, debridement biopsies, orthogonal histopathology, and magnetic resonance laparotomy. There is no requirement for a pneumatic instrument while doing ultrasonic strong segment injection biopsies, which are recommended by many medical professionals. Reports on the types of biopsies would contain the following:
  - The stage of cancer is defined by the rate of cell growth and division. Malignancies of excellent grade (rank 4) were more diverse than malignancies of poorer quality (rank 1). Malignancies of lesser quality were more clearly characterized [79].
- The histochemical, which might vary based on the susceptibility of the carcinoma to hormones or the overexpression of the hormone epidermal growth factor<sup>2</sup> within the carcinoma [61].
- 
- A potentiality with chemoradiotherapy and also the occurrence among persons who have acute tumours may be predicted using the clinical diagnostic chest relapse Index. When assessing malignancy, tumour, node metastasis (TNM) categorization and organisations are both taken into consideration. A significant number of women with a histological form of breast cancer need to undergo testing for Brca 1 or 2 alterations. Cowden disease and Li-Fraumeni disease are both associated with an increased risk of developing chest cancer [80]. Individuals who have a family history of chest, prostate, ovarian, colorectal, thyroid, or endometriosis cancers may be candidates for a more in-depth genetic evaluation [81].

### 3.6. Surgery

Comment [MF11]: BRCA

Surgery is one of the most often used treatments for tumours. This information might be kept in conjunction with further medications such as radiation, surgery, and targeted therapy[82]. There are two distinct forms of chest therapy: the breast-conserving procedure known as a lumpectomy and the traditional mastectomy [83].

- **Mastectomy:** The entirety of the chest was disassembled and discarded [84].

**Radiation treatment:** In radiation and chemotherapy, exceptionally high levels of emission are utilised in order to eradicate malignant tissue. The process of radiotherapy involves the continual destruction of tumours. Many will inevitably pass away due to the fact that the tissues do not have a measurement for improvement itself among the regular medication [85, 86]. The use of chemicals in a therapeutic setting with the intention of eliminating malignant tissue is known as chemotherapy. To a modest degree, cancerous tissues participate in the proliferation, reproduction, and migration of cancer cells to other parts of the body caused by chemotherapy and radiation. The treatment, known as chemotherapy, has the potential to cause side effects such as nausea, vomiting, mouth ulcers, exhaustion, and an increased risk of infection or baldness. There is a possibility that some cancer medications will have an effect on male sperm, which might affect the fertility potential of the patient. Therefore, during treatment, your cycles might not occur, but when they do, you might experience fertility problems [87, 88].

- **A treatment based on hormones:**

The proteins oestrogen and progesterone found at the covers of many cancer cells can be found in these cells. Cancers that include oestrogen protein can also manifest in another prevalent form. This connection between hormones (oestrogen or progesterone) inside a unique protein on the tumour might accelerate the expansion of carcinoma. Pharmacological therapies are used to regulate hormone kinase cancer by lowering progesterone or oestrogen levels inside the body and reducing their impact on malignant tissues. This is accomplished by inhibiting the body's production of these hormones.

- **Aromatase inhibitor**

Comment [MF12]: Reference?

Comment [MF13]: correct

Human beings exposed to these inhibitors will not be able to produce hormones. Only women who have never given birth can use them. climacteric signs like heartburn with sexual dysfunction, excess weight, premature climacteric (which are irreversible when the ovaries are eliminated), and muscle and joint problems could be among the adverse reactions caused by hormonal treatment [89]. The adverse reactions caused by hormonal treatment vary depending on the substance or form of the hormonal therapy that is used.

- **Treatment using biological agents**

It is a type of treatment that makes use of the immunological reactions of human patients. There are several different therapy techniques that may be used to manage carcinoma. Herceptin's successor, trastuzumab, was used more often and extensively. Only females are capable of storing trastuzumab because only females have human epidermal growth factor receptor-positive invasive carcinoma, which is a kind of cancer that has spread beyond milk ducts and lobules and into many other places where malignant cells are present. In order to exert more control over the enzyme human epidermal growth factor2 (EGF2), trastuzumab may be used in conjunction with some chemotherapy drugs as well as after their administration. Common cold symptoms (heat, chills, or vomiting), constipation, lethargy, migraine, redness, or discomfort/sensitivity only upon treated region are all possible consequences with therapeutic intervention[90]. Other possible complications include redness, discomfort/sensitivity just upon treated area, and lethargy[91].

### **Conclusions and Future Perspectives:**

Over the course of the past two decades, treatment for breast cancer has evolved to become more personalised and targeted. The molecular subtyping of breast cancer provides the basis for the many precision therapeutic techniques that are currently being developed. The escalation and de-escalation of treatment in line with the biology of the tumour and early prognostic indicators will play a more prominent role in future therapeutic methods. Individualization of therapy for each patient will also play a larger role. In conjunction with subtyping-based umbrella studies[92], additional classification of the many breast cancer subtypes that already exist (such as TNBC) may result in an improvement in the prognosis of the illness. In addition, there is an ongoing requirement for the research and development of innovative treatments for both early and advanced stages of breast cancer. The overarching objective of ongoing study is to get an understanding of the factors that contribute to resistance to treatment as well as methods for

overcoming this phenomenon. Single-cell technologies will provide insight on the interactions that occur between tumours and the microenvironments in which they reside. These technologies may also assist in the development of novel treatment targets and biomarkers. For instance, a single-cell analysis suggested that in TNBC, the fraction of the T cell subgroup that was positive for CXCL13 was a strong predictor of how effectively the therapies against PD-L1 performed. This was seen in patients who had the cancer known as triple-negative breast cancer.

The primary focus in breast cancer surgery currently is on de-escalation. In the future, surgical methods will place a greater emphasis on understanding the biology of the cancer and will employ more customised treatment strategies. In the coming years, it will be necessary to find answers to two significant concerns surrounding the treatment of breast cancer. Patients who have a pCR after undergoing neoadjuvant therapy may be able to forgo breast surgery. The second question is whether or not certain people can completely avoid undergoing axillary surgery for both the staging and treatment stages of the disease. These are very important issues, yet running randomised controlled trials to get answers to them might be difficult because of concerns about people's safety, which highlights the need for international cooperation. In order to find a solution that strikes a balance between the potential for a decrease in undesirable occurrences and an increase in the danger of recurrence, each individual situation needs to be thoroughly analysed and addressed. It is essential that clinical trial settings be utilised in order to investigate any potential de-escalation strategies or concepts.

#### References

1. *Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017*. Lancet, 2018. **392**.
2. Rozenblatt-Rosen, O., et al., *The human tumor atlas network: Charting tumor transitions across space and time at single-cell resolution*. Cell, 2020. **181**.
3. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2020*. CA: A Cancer Journal for Clinicians, 2020. **70**.
4. Thomas, F., et al., *Evolutionary ecology of organs: A missing link in cancer development?* Trends Cancer, 2016. **2**.

5. Tomasetti, C., L. Li, and B. Vogelstein, *Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention*. Science, 2017. **355**.
6. Zahir, N., et al., *Characterizing the ecological and evolutionary dynamics of cancer*. Nature Genetics, 2020. **52**.
7. Arbyn, M., et al., *Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis*. Lancet Glob Health, 2020. **8**.
8. Armitage, E.G. and M. Ciborowski, *Applications of metabolomics in cancer studies*. Adv Exp Med Biol, 2017. **965**.
9. Baker, S.G., *Cancer screening markers: a simple strategy to substantially reduce the sample size for validation*. Med Decis Mak, 2019. **39**.
10. Wright, A.A., et al., *Associations between palliative chemotherapy and adult cancer patients' end of life care and place of death: prospective cohort study Associations between palliative chemotherapy and adult cancer patients' end of life care and place of death: prospective cohort study*. BMJ., 2014. **348**.
11. Wise, P.H., *Cancer drugs, survival, and ethics*. BMJ., 2016. **355**.
12. Ventola, C.L., *Cancer Immunotherapy, Part 2: Efficacy, Safety, and Other Clinical Considerations*. P T., 2017. **42**.
13. Temel, J.S., et al., *Longitudinal Perceptions of Prognosis and Goals of Therapy in Patients With Metastatic Non–Small-Cell Lung Cancer: Results of a Randomized Study of Early Palliative Care*. J. Clin. Oncol., 2011. **29**.
14. Rauniyar, A., et al., *Federated Learning for Medical Applications: A Taxonomy, Current Trends, Challenges, and Future Research Directions*. 2022.
15. Witkiewicz AK, Wright TC, Ferenczy A et al (2011) Carcinoma and other tumors of the cervix. *Blaustein's pathology of the female genital tract, vol 6, pp 253–303*.
16. Harada, T., N. Sukoh, and N. Hakuma, *Pulmonary blastoma within bronchioloalveolar cell carcinoma*. Respiriology, 2006. **11**.
17. Isaacs R (2009) *Lymphosarcoma cell leukemia. Landmark Papers in Internal Medicine: the first 80 years of annals of internal medicine, vol 441*.
18. Fonseca R, Valdez R (2002) *Plasma cell neoplasms. Diagnostic Techniques in Hematological Malignancies 244:30–36*.

19. Cupedo T, Coles MC, Veiga-Fernandes H (2011) Development and structure of lymph nodes in humans and mice. *Developmental Biology of Peripheral Lymphoid Organs*, pp 59–74.
20. Maresso, K.C., et al., *Molecular cancer prevention: current status and future directions*. CA: a cancer journal for clinicians, 2015. **65**(5): p. 345-383.
21. Anaya, J., et al., *A pan-cancer analysis of prognostic genes*. PeerJ, 2016. **3**: p. e1499.
22. Lebeau, A., et al., *Invasive breast cancer: the current WHO classification*. Der Pathologe, 2014. **35**: p. 7-17.
23. Cho, W.C., *Contribution of oncoproteomics to cancer biomarker discovery*. Molecular cancer, 2007. **6**: p. 1-13.
24. Goossens, N., et al., *Cancer biomarker discovery and validation*. Translational cancer research, 2015. **4**(3): p. 256.
25. Brenner, D.R., et al., *Breast cancer survival among young women: a review of the role of modifiable lifestyle factors*. Cancer causes & control, 2016. **27**: p. 459-472.
26. Dobrolecki, L.E., et al., *Patient-derived xenograft (PDX) models in basic and translational breast cancer research*. Cancer and Metastasis Reviews, 2016. **35**: p. 547-573.
27. Nardin, S., et al., *Breast Cancer Survivorship, Quality of Life, and Late Toxicities*. Front Oncol, 2020. **10**: p. 864.
28. Bellanger, M., et al., *Are Global Breast Cancer Incidence and Mortality Patterns Related to Country-Specific Economic Development and Prevention Strategies?* J Glob Oncol, 2018. **4**: p. 1-16.
29. Francies, F.Z., et al., *Breast cancer in low-middle income countries: abnormality in splicing and lack of targeted treatment options*. Am J Cancer Res, 2020. **10**(5): p. 1568-1591.
30. Religioni, U., *Cancer incidence and mortality in Poland*. Clinical Epidemiology and Global Health, 2020. **8**(2): p. 329-334.
31. Lakhani, S.R., et al., *WHO Classification of Tumours of the Breast*. 2012.
32. Lima, S.M., R.D. Kehm, and M.B. Terry, *Global breast cancer incidence and mortality trends by region, age-groups, and fertility patterns*. EClinicalMedicine, 2021. **38**: p. 100985.

33. Kudela, E., et al., *Breast cancer in young women: status quo and advanced disease management by a predictive, preventive, and personalized approach*. *Cancers*, 2019. **11**(11): p. 1791.
34. Torre, L.A., et al., *Global cancer in women: burden and trends* *global cancer in women: burden and trends*. *Cancer epidemiology, biomarkers & prevention*, 2017. **26**(4): p. 444-457.
35. Brinton, L.A., et al., *Menstrual factors and risk of breast cancer*. *Cancer Invest*, 1988. **6**(3): p. 245-54.
36. de Blok, C.J., et al., *Breast cancer risk in transgender people receiving hormone treatment: nationwide cohort study in the Netherlands*. *Bmj*, 2019. **365**.
37. Cancer, C.G.o.H.F.i.B., *Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies*. *The lancet oncology*, 2012. **13**(11): p. 1141-1151.
38. Sisti, J.S., et al., *Reproductive risk factors in relation to molecular subtypes of breast cancer: Results from the nurses' health studies*. *Int J Cancer*, 2016. **138**(10): p. 2346-56.
39. Ferlay, J., et al., *Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012*. *International journal of cancer*, 2015. **136**(5): p. E359-E386.
40. *TNM classification of malignant tumours*. 2011, Hoboken, NJ: Wiley.
41. Abramson, V.G., et al., *Subtyping of triple-negative breast cancer: implications for therapy*. *Cancer*, 2015. **121**.
42. Ades, F., et al., *Luminal B breast cancer: molecular characterization, clinical management, and future perspectives*. *J Clin Oncol*, 2014. **32**.
43. Allison, K.H., et al., *Estrogen and progesterone receptor testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists guideline update*. *Arch Pathol Lab Med*, 2020. **144**.
44. Amin, M.B., et al., *The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging*. *CA Cancer J Clin*, 2017. **67**.
45. Anders, C.K. and L.A. Carey, *Biology, metastatic patterns, and treatment of patients with triple-negative breast cancer*. *Clin Breast Cancer*, 2009. **9**.

46. Arpino, G., et al., *Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome*. Breast Cancer Res, 2004. **6**.
47. Asselain, B., et al., *Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials*. Lancet Oncol, 2018. **19**.
48. Badve, S., et al., *Basal-like and triple-negative breast cancers: a critical review with an emphasis on the implications for pathologists and oncologists*. Mod Pathol, 2011. **24**.
49. Bae, S.Y., et al., *Mucinous carcinoma of the breast in comparison with invasive ductal carcinoma: clinicopathologic characteristics and prognosis*. J Breast Cancer, 2011. **14**.
50. Choi, J., W.H. Jung, and J.S. Koo, *Clinicopathologic features of molecular subtypes of triple negative breast cancer based on immunohistochemical markers*. Histol Histopathol, 2012. **27**.
51. Curtis, C., et al., *The genomic and transcriptomic architecture of 2, 000 breast tumours reveals novel subgroups*. Nature, 2012. **486**.
52. Dowsett, M., et al., *Integration of clinical variables for the prediction of late distant recurrence in patients with estrogen receptor–positive breast cancer treated with 5 years of endocrine therapy: CTS5*. J Clin Oncol, 2018. **36**.
53. Sparano, J.A., et al., *Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer*. N Engl J Med, 2018. **379**.
54. Bianchini, G., et al., *Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease*. Nat Rev Clin Oncol, 2016. **13**(11): p. 674-690.
55. Bjarnadottir, O., et al., *Targeting HMG-CoA reductase with statins in a window-of-opportunity breast cancer trial*. Breast Cancer Res Treat, 2013. **138**(2): p. 499-508.
56. Blanco, E., et al., *Colocalized delivery of rapamycin and paclitaxel to tumors enhances synergistic targeting of the PI3K/Akt/mTOR pathway*. Mol Ther, 2014. **22**(7): p. 1310-1319.
57. Bonnefoi, H., et al., *A phase II trial of abiraterone acetate plus prednisone in patients with triple-negative androgen receptor positive locally advanced or metastatic breast cancer (UCBG 12-1)*. Ann Oncol, 2016. **27**(5): p. 812-8.
58. Chan, S.M., et al., *Notch signals positively regulate activity of the mTOR pathway in T-cell acute lymphoblastic leukemia*. Blood, 2007. **110**(1): p. 278-86.

59. *TNM classification of malignant tumours*. 2017, John Wiley and Sons: Chichester.
60. Giuliano, A.E., et al., *Breast cancer—major changes in the American Joint Committee on Cancer eighth edition cancer staging manual*. CA Cancer J Clin, 2017. **67**.
61. Ogawa, Y., et al., *Immunohistochemical assessment for estrogen receptor and progesterone receptor status in breast cancer: analysis for a cut-off point as the predictor for endocrine therapy*. Breast cancer, 2004. **11**: p. 267-275.
62. Hendry, S., R. Salgado, and T. Gevaert, *Assessing tumor-infiltrating lymphocytes in solid tumors: a practical review for pathologists and proposal for a standardized method from the International Immunooncology Biomarkers Working Group: part 1: assessing the host immune response, TILs in invasive breast carcinoma and ductal carcinoma in situ, metastatic tumor deposits and areas for further research*. Adv Anat Pathol, 2017. **24**.
63. Diaz, L.K. and N. Sneige, *Estrogen receptor analysis for breast cancer: current issues and keys to increasing testing accuracy*. Advances in anatomic pathology, 2005. **12**(1): p. 10-19.
64. Hortobagyi, G., et al., *Breast*, in *AJCC cancer staging manual*, M.B. Amin, S.B. Edge, and F.L. Greene, Editors. 2017, Springer: New York.
65. Shi, F., et al., *One-step nucleic acid amplification assay is an accurate technique for sentinel lymph node biopsy of breast cancer patients: a meta-analysis*. Br J Cancer, 2017. **117**.
66. Davies, C., et al., *Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials*. Lancet, 2011. **378**(9793): p. 771-84.
67. Zombori, T., et al., *Evaluation of anatomic and prognostic stages of breast cancer according to the 8th edition of the TNM staging system—retrospective analysis based on data from deceased patients once diagnosed with breast cancer*. Orv Hetil, 2017. **158**.
68. Wazir, U., et al., *Pleomorphic lobular carcinoma in situ: current evidence and a systemic review*. Oncol Lett, 2016. **12**.
69. Osborne, C.K., *Tamoxifen in the treatment of breast cancer*. N Engl J Med, 1998. **339**(22): p. 1609-18.

70. Regan, M.M., et al., *Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8· 1 years median follow-up*. *The lancet oncology*, 2011. **12**(12): p. 1101-1108.
71. Makki, J., *Diversity of breast carcinoma: histological subtypes and clinical relevance*. *Clinical medicine insights: Pathology*, 2015. **8**: p. CPath. S31563.
72. Rakha, E. and I.O. Ellis, *An overview of assessment of prognostic and predictive factors in breast cancer needle core biopsy specimens*. *Journal of clinical pathology*, 2007. **60**(12): p. 1300-1306.
73. Wysocka, J., *New WHO classification of breast tumours—as published in 2019*. *Nowotwory*. *Journal of Oncology*, 2020. **70**(6): p. 250-252.
74. Tan, P.H., et al., *WHO classification of tumours editorial board. The 2019 world health organization classification of tumours of the breast*. *Histopathology*, 2020. **77**(2): p. 181-185.
75. Elston, C.W. and I.O. Ellis, *Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up*. *Histopathology*, 1991. **19**(5): p. 403-410.
76. Amin, M.B., et al., *The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more “personalized” approach to cancer staging*. *CA: a cancer journal for clinicians*, 2017. **67**(2): p. 93-99.
77. de Boer, M., et al., *Breast cancer prognosis and occult lymph node metastases, isolated tumor cells, and micrometastases*. *Journal of the National Cancer Institute*, 2010. **102**(6): p. 410-425.
78. Tan, L.K., et al., *Occult axillary node metastases in breast cancer are prognostically significant: results in 368 node-negative patients with 20-year follow-up*. *Journal of Clinical Oncology*, 2008. **26**(11): p. 1803-1809.
79. Goldhirsch, A., et al., *Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009*. *Annals of oncology*, 2009. **20**(8): p. 1319-1329.

80. Howell, A., et al., *Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer*. *Lancet*, 2005. **365**(9453): p. 60-2.
81. Fisher, B., et al., *Relative worth of estrogen or progesterone receptor and pathologic characteristics of differentiation as indicators of prognosis in node negative breast cancer patients: findings from National Surgical Adjuvant Breast and Bowel Project Protocol B-06*. *J Clin Oncol*, 1988. **6**(7): p. 1076-87.
82. Hähnel, R., T. Woodings, and A. Brian Vivian, *Prognostic value of estrogen receptors in primary breast cancer*. *Cancer*, 1979. **44**(2): p. 671-675.
83. Moja, L., et al., *Trastuzumab containing regimens for early breast cancer*. *Cochrane database of systematic reviews*, 2012(4).
84. Piccart-Gebhart, M.J., et al., *Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer*. *New England Journal of Medicine*, 2005. **353**(16): p. 1659-1672.
85. Smith, I., et al., *2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial*. *The lancet*, 2007. **369**(9555): p. 29-36.
86. Romond, E.H., et al., *Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer*. *New England journal of medicine*, 2005. **353**(16): p. 1673-1684.
87. Perez, E., et al., *Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer*. *Journal of clinical oncology*, 2007. **25**(18\_suppl): p. 512-512.
88. Smith, A.E., et al., *HER2 + breast cancers evade anti-HER2 therapy via a switch in driver pathway*. *Nat Commun*, 2021. **12**(1): p. 6667.
89. de Azambuja, E., et al., *Ki-67 as prognostic marker in early breast cancer: a meta-analysis of published studies involving 12,155 patients*. *Br J Cancer*, 2007. **96**(10): p. 1504-13.
90. Curigliano, G., et al., *De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017*. *Annals of Oncology*, 2017. **28**(8): p. 1700-1712.

91. Burstein, H.J., et al., *Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen International Consensus Guidelines for the primary therapy of early breast cancer 2019*. *Annals of Oncology*, 2019. **30**(10): p. 1541-1557.
92. Zhang, Y., et al., *Single-cell analyses reveal key immune cell subsets associated with response to PD-L1 blockade in triple-negative breast cancer*. *Cancer Cell*, 2021. **39**(12): p. 1578-1593.e8.

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