# An Overview about Early breast cancer outcome & adjuvant chemotherapy regimens

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**Abstract**

**Background**

Breast cancers are considered as early operable if there is clinically no extension of the primary tumor/axillary lymph node disease to skin/chest wall or in the absence of extra-axillary nodes.The 15th St. Gallen International Breast Cancer Conference 2017 in Vienna, Austria endorsed gene expression signatures that permit avoidance of chemotherapy in many patients with ER positive breast cancer. The St. Gallen Panel recognized that recommendations are not intended for all patients, but rather to address the clinical needs of the majority of common presentations. Individualization of adjuvant therapy means adjusting to the tumor characteristics & patient comorbidities.Historically, the DBCG 77B trial demonstrates that oral single-agent cyclophosphamide significantly reduces the risk of recurrence and mortality as compared with no systemic therapy in pre-menopausal patients with high-risk early stage breast cancer. While DBCG 89D trial showed an incremental benefit in DFS and OS from substituting methotrexate with epirubicin in the classic CMF protocol.

**Keywords:**Early breast cancer, chemotherapy regimens Stenting, High Surgical Risk Patients.

## INTRODUCTION

For many years, breast cancer has had the highest incidence of all cancers in women worldwide. Patients have better survival compared with more fatal cancers possibly because the breast tissue is physically not a necessary organ for human survival. bounds have been made in terms of this endeavor, especially in recent years. Mastectomy and chemotherapy have greatly improved the survival of breast cancer patients and more elegant forms of surgical procedures are now being applied to minimize the post-treatment psychological impact. However, without fully understanding the underlying mechanism and pathogenesis, the efficiency of prevention and treatment will always be limited (Feng et al., 2018).

Breast cancer is the most commonly diagnosed cancer and is the leading cause of cancer death in women worldwide. Several factors increase the risk of breast cancer development, including patient characteristics, lifestyle habits, and predisposing genetic mutations. ( Nicole M., 2022 )

Epidemiology

Worldwide, breast cancer is the most common type of cancer among women. In women, breast cancer accounts for 29% of new cases of cancer and 14% of cancer deaths, second only to lung cancer as a

cause of cancer-specific death. Approximately 1% of breast cancers occur in males and 90% of these are estrogen receptor (ER)-positive. (Gucalp et al., 2019)

According to global cancer statistics BC accounts for 16.4% of all cancers and 32.4% of female malignancies in Egypt and is the most prevalent cancer among Egyptian women. (Jemal A. et al., 2020)

Large variations in incidence, mortality, and survival, which may be a result of several underlying complex factors, including age, ethnicity, diet, and lifestyles (including reproductive issues such as age at first birth and breastfeeding). Breast cancer is increasing in less-developed countries, supposedly related to changes in lifestyle factors (Bray et al., 2018)

Since 1990, the annual death rate from breast cancer has been diminishing by roughly 2.2% per year. Median survival of patients with MBC has improved in recent years beyond 30 months, although survival varies significantly by breast cancer subtype. A number of newer active agents have recently been founded against breast cancer, including third-generation aromatase inhibitors, novel anti-microtubule chemotherapy agents, and biologic agents such as lapatinib, pertuzumab, and everolimus. Despite these advances, breast cancer remains the second leading cause of cancer death in women (Rakha and Pareja, 2020).

I. Risk factors for breast cancer

1. Genetic Predispositions as Important Risk Factors of Breast Cancer

Overall, about 5-10% of breast cancers are linked to gene mutations inherited from a parent. The most common cause of hereditary breast cancer is an inherited mutation in the BRCA1 or BRCA2 gene. Statistically, women with a BRCA1 mutation have a 55-65% lifetime risk of developing breast cancer. For women with a BRCA2 mutation, the lifetime risk is 45%. On average, a woman with a BRCA1 or BRCA2 gene mutation has about 70% chance of getting breast cancer by age 80. The effect of the mutation is related to how many other family members have breast cancer, as breast cancer risk goes up if more family members are affected. (Ossa and Torres, 2016).

Women with one of these two mutations are also more likely to be diagnosed with breast cancer at a younger age, as well as to have cancer in both breasts. (Godet and Gilkes, 2017).

2. "Non-Genetic" Risk Factors of Breast Cancer

*i.* *Family history of breast cancer*:

While less than 15% of women with breast cancer have a family member with this disease, women who do have close blood relatives with breast cancer have a higher risk. For instance, having a first-degree relative (mother, sister, or daughter) with breast cancer almost doubles a woman's risk while having two first-degree relatives with the disease increases the woman's risk about 3-fold. Interestingly, women with a father or brother who have breast cancer also have a higher risk of breast cancer. Within the context on an individual, a woman with cancer in one breast has a higher risk of developing a new cancer in the other breast or in another part of the same breast (Feng et al., 2018).

*ii.* *Race and ethnicity*:

In general, Caucasian women are more likely to develop breast cancer than African-American women. Furthermore, African-American women are more likely to die from breast cancer at any age. Other races such as Asian, Hispanic, and Native American women have a lower risk of developing and dying from breast cancer (Winters et al., 2017).

*Certain benign breast conditions:*

Women with dense breasts on mammogram have a risk of breast cancer that is about 1.5 to 2 times that of women with average breast density even though multi factors play a role in determining breast density, such as age, menopausal status, the use of certain drugs (such as menopausal hormone therapy) and pregnancy. Certain non-proliferative lesions may marginally affect breast cancer risk. These non-proliferative lesions include fibrosis and/or simple cysts, mild hyperplasia, adenosis, phyllodes tumor, single papilloma, duct ectasia, periductal fibrosis, squamous and apocrine metaplasia, epithelial-related calcifications, other tumors (lipoma, hamartoma, hemangioma, neurofibroma, adenomyoepithelioma), or mastitis (Feng et al., 2018).

*Certain proliferative breast lesions:*

Some proliferative lesions without atypia seem to raise a woman's risk of breast cancer slightly. Examples of such proliferative lesions are ductal hyperplasia, fibroadenoma, sclerosing adenosis, papillomatosis or radial scar. However, certain proliferative lesions with atypia in the ducts or lobules of the breast tissue will increase breast cancer risk 4 to 5-fold; and these include atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) (Arango et al., 2018).

*Lobular carcinoma in situ (LCIS) or lobular neoplasia:*

LCIS is traditionally grouped with ductal carcinoma in situ (DCIS) as a non-invasive breast cancer, while recent updates in the field consider LCIS to be benign. However, LCIS differs from DCIS in that it usually does progress to become invasive cancer if it is not treated, and also have a much higher risk of developing cancer in either breast (Feng et al., 2018).

*Chest radiation therapy:*

Women, who were treated with radiation therapy to the chest for another cancer when they were younger, especially have higher risk for developing breast cancer. The impact of this factor on increasing risk is highest if the individual had radiation as a teen or young adult, when the breasts were still developing. Conversely, radiation treatment after age 40 does not seem to increase breast cancer risk. (Tabár et al., 2019)

*Exposure to diethylstilbestrol (DES):*

From 1940s through early 1970s some pregnant women were given an estrogen-like drug DES because it was thought to lower the incidence of miscarriage. These women have a slightly increased risk of breast cancer, and women whose mothers took DES during pregnancy may also have a slightly higher risk of breast cancer (Feng et al., 2018).

3. Lifestyle and Personal Behavior-Related Risk Factors of Breast Cancer

Vast majority (about 85%) of breast cancers occur in women without apparent family history of breast cancer. These cancers may be caused by genetic mutations that occur as a result of the aging process and lifestyle-related risk factors, rather than inherited mutations (Widschwendter et al., 2018).

*Birth control and contraceptives:*

Many birth control methods use hormones, which may increase breast cancer risk. Women using oral contraceptives have a slightly higher risk of breast cancer than women who have never used them, although the risk seems to go back to normal over time once the regimen is stopped. (Suter and Pagani, 2018).

*Hormone replacement therapy (HRT) after menopause:*

The hormone estrogen (often combined with progesterone) has been used to relieve symptoms of menopause and to prevent osteoporosis. Postmenopausal combined hormone therapy increases the risk of breast cancer, the chances of dying from breast cancer, and the likelihood that the cancer may be found only at a more advanced stage. This increase in risk is usually seen with as little as two years of use. However, the increased risk from combined and seemingly returns to that of the general population within five years of stopping HRT (Kanis et al., 2019).

*Excessive alcohol consumption*:

Drinking alcohol is clearly linked to an increased risk of breast cancer, and the increase in risk caused by this factor correlates with the amount of alcohol consumed. For example, women who have two to three drinks a day have approximately 20% higher risk of breast cancer. (Wiseman and Klein, 2019).

*Significant overweight or obese:*

Before menopause women's ovaries make most of the body's estrogen, while fat tissue makes only a small amount. However, when the ovaries stop making estrogen after menopause, most of a woman's estrogen comes from fat tissue. Thus, having more fat tissue after menopause will raise estrogen levels and increase breast cancer risk. Furthermore, being overweight tends to lead to higher blood insulin levels, and higher insulin levels are linked to certain cancers, including breast cancer. Nonetheless, the link between body weight and breast cancer risk is complex and remains to be fully understood (Feng et al., 2018).

*Not having children or not breastfeeding:*

Women who have not had children or who have their first child after age 30 have a slightly higher overall risk for breast cancer. Conversely, having multiple pregnancies and/or becoming pregnant at an early age reduce breast cancer risk. Nonetheless, pregnancy seems to have different effects on different types of breast cancer, and pregnancy seems to increase risk for triple-negative breast cancer. It has been suggested that breastfeeding may slightly lower breast cancer risk, especially if it is continued for 1.5 to 2 years. A possible explanation for this effect is that breastfeeding reduces woman's total number of lifetime menstrual cycles (Victora et al., 2016).

*Starting menstruation early or stopping menopause after age 55:*

Women will have more menstrual cycles if they start menstruating early, especially before age 12, and thus they will have a longer lifetime exposure to the hormones estrogen and progesterone, leading to a slightly higher risk of breast cancer. Similarly, women will have more menstrual cycles if they go through menopause later, especially after age 55, and also have a longer lifetime exposure to estrogen and progesterone with a higher risk of breast cancer (Trabert et al., 2020).

*Lack of physical activity:*

Growing evidence indicates that regular physical activity, especially in women past menopause, may reduce breast cancer risk. It is not completely clear how physical activity might reduce breast cancer risk, but it may be due to the fact that activity levels affect body weight, inflammation, hormones, and energy balance (Ulrich et al., 2018).

The widespread use of adjuvant chemotherapy in patients diagnosed with early-stage estrogen receptor (ER)-positive breast cancer has contributed to the reduction of breast cancer-related mortality and the estimated absolute risk reduction is between 5 and 15%. However, not all patients benefit equally from adjuvant chemotherapy. So, Methods to identify and select patients who benefit most and those who benefit little from chemotherapy are important to reduce unnecessary exposure to cytotoxic therapies and their associated side effects.( Zhen R. et al.,2018)

The regimens used in this setting generally included anthracyclines (doxorubicin, epirubicin) and/or taxanes(paclitaxel, docetaxel), which are the two most active classes of cytotoxic agents for both early and advanced stage breast cancer. (Cao et al., 2017)

Oncotype DX

Oncotype DX is a multigene assay consists of 21 genes of recurrence score. Estrogen (ER , PGR , BCL2 & Scube2) ,HER2 ( HER2 & GRB7) ,proliferation (Ki67% ,STK15 , suviven ,MYBL2 & CCBB1), CD68 ,invasion (MMP11 & CTSL2), BAG1 , reference (GUS ,GAPDH ,TFRC ,RPLPO &ACTB). (Paik S. et al.,2004)

Genomic assays such as Oncotype DX have changed the land-scape for the treatment of ER-positive early breast cancer. In a USA-based study, there has been a 13% decline in the use of adjuvant chemotherapy in 2006–2008. ( Hassett M. et al., 2012)

With use of a panel of 16 cancer-related genes and 5 reference genes, the likelihood of developing distant recurrence in ER-positive early stage breast cancer is calculated as a recurrence score (RS) ranging from 0 to 100. RS can also be subdivided into three risk categories: low (<18), intermediate (18–30), and high (>30) scores. (Jeniffer E. et al., 2011)

*Adjuvant hormonal treatment*

It has been well documented that estrogen plays a critical role in breast cancer development and is a major target for treatment. For many years, tamoxifen has been the gold standard for adjuvant hormonal therapy in breast cancer patients. In addition to the newer products targeting different mechanisms to suppress estrogen production, patients now have many decisions regarding their care. Agents such as luteinizing hormone releasing hormone (LHRH) agonists can suppress ovarian function in premenopausal patients. With the advent of third generation aromatase inhibitors (anastrozole, letrozole and exemestane) toxicities have been documented to be less and in some cases they are more efficacious than the standard, tamoxifen. (Kellie L. et al., 2004)

For women with higher risk tumors, The 15th St. Gallen International Breast Cancer Conference 2017 Panel escalated recommendations for adjuvant endocrine treatment to include ovarian suppression in premenopausal women, and extended therapy for postmenopausal women. However, low-risk patients can avoid these treatments. (Curigliano G. et al., 2017)

The EBCTCG trial demonstrated that DFS and OS were better in those women who received ovarian ablation (i.e.goserelin) compared with those patients who did not receive any adjuvant treatment. When compared with chemotherapy (CMF-like regimens), ovarian ablation showed equivalency, with a better toxicity profile. (Gray R., 2019)

ATAC trial provided anastrozole as another alternative to tamoxifen therapy in postmenopausal women. This drug has resulted in reductions in the risk of recurrence and an overall better safety profile than tamoxifen. Results of the MA-17 trial have demonstrated a benefit with letrozole used sequentially after 5 years of tamoxifen. The data in the exemestane and anastrozole trials for 2 to 3 years after 2 to 3 years of tamoxifen have demonstrated that changing therapy to an AI instead of completing 5 years of tamoxifen can significantly reduce the risk of recurrence.( Ivana s. et al., 2008 )

*4- Adjuvant targeted therapy*

Increased knowledge of the biologic diversity of breast cancer has been accompanied by increased efforts to individualize breast cancer treatment based on the underlying molecular features of each tumor. Approximately 15% to 20% of early breast cancers have amplification of the human epidermal receptor-2 (HER-2) gene, with resultant overexpression of the HER-2 protein. Tumors that over express this protein are imbued with more aggressive qualities, including enhanced growth and

proliferation, increased invasive and metastatic capability, and stimulation of angiogenesis. (Mackey J. et al., 2009)

Patients should be offered 1 year total of adjuvant trastuzumab, with regular assessments of cardiac function during that period. And Patients with HER2-positive breast cancer with pathologic invasive residual disease at surgery after standard preoperative chemotherapy and HER2-targeted therapy should be offered 14 cycles of adjuvant T-DM1, unless there is disease recurrence or unmanageable toxicity. There are no data to guide the duration of pertuzumab in patients who received neoadjuvant pertuzumab and achieved a pathologic complete response. (Neelima D. et al., 2021)

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Historically , the DBCG 77B trial demonstrates that oral single-agent cyclophosphamide significantly reduces the risk of recurrence and mortality as compared with no systemic therapy in pre-menopausal patients with high-risk early stage breast cancer. While DBCG 89D trial showed an incremental benefit in DFS and OS from substituting methotrexate with epirubicin in the classic CMF protocol. (Ejlertsen B. et al.,2016)

EBCTCG meta-analysis demonstrates that a further reduction in breast cancer mortality appeared from the addition of a taxane to a standard AC, while the substitution of cycles or drugs with a taxane was not associated with a reduction in mortality. (Haidenger R. et al., 2019)

The administration of trastuzumab after chemotherapy permits the application of their findings to the wide variety of chemotherapy regimens used throughout the world. The results of HERA trial indicate that one year of adjuvant trastuzumab should be considered a standard on completion of locoregional therapy and neoadjuvant or adjuvant chemotherapy for women who fulfill the study eligibility criteria used in the HERA trial. This study indicated that adding trastuzumab to chemotherapy had improved overall survival by 6% (79% received chemotherapy plus trastuzumab VS 73% received chemotherapy only) (Mery et al., 2019).

Another study was done by Slamon and Breast cancer International Research group published at N Engl J Med, randomly assigned 3222 women with HER2-positive early-stage breast cancer to receive doxorubicin and cyclophosphamide followed by docetaxel every 3 weeks (AC-T), the same regimen plus 52 weeks of trastuzumab (AC-T plus trastuzumab), or docetaxel and carboplatin plus 52 weeks of trastuzumab (TCH). The estimated disease-free survival rates at 5 years were 75% among patients receiving AC-T, 84% among those receiving AC-T plus trastuzumab, and 81% among those receiving TCH. Estimated rates of overall survival were 87%, 92%, and 91%, respectively. (Tate et al., 2021).

For patients with hormone-receptor negative disease, the absolute risk of distant recurrence as a first event is reduced by 9.6% at 7 years, after which distant recurrence from breast cancer is unlikely that was a presented data from the final planned joint analysis of overall survival from the NSABP B-31 and NCCTG N9831 trials at the 35th Annual San Antonio Breast Cancer Symposium (SABCS) (Corbaux et al., 2022).

In a large randomized adjuvant clinical trial comparing an anthracycline-based regimen in combination with trastuzumab with a non–anthracycline-based regimen in combination with trastuzumab, no significant differences in efficacy were found, but there was a higher rate of cardiac dysfunction in patients receiving the anthracycline-based regimen(Ferraro et al., 2022).

KATHERINE trial (A Study of Trastuzumab Emtansine vs Trastuzumab as Adjuvant Therapy in Patients With HER2-Positive Breast Cancer Who Have Residual Tumor in the Breast or Axillary Lymph Nodes Following Preoperative Therapy) trial is a randomized clinical trial comparing the efficacy and safety of trastuzumab emtansine vs trastuzumab as adjuvant therapy for patients with HER2-positive breast cancer who have residual tumor in the breast or axillary lymph nodes after neoadjuvant therapy(Bulska et al., 2022).

The KATHERINE study has shown that there was 50% reduction in invasive disease recurrence when treated with T-DM1 in the adjuvant setting. (llavarasivanidassane et al., 2020).

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