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Breast Cancer: A Review on Prognosis and Treatment Methods

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Abstract: Breast cancer is a concerning issue among women in general. In recent decades, breast cancer research has evolved quickly. Recent findings offer more treatment choices, better long-term survival for women with breast cancer, and the chance to move towards cures in advanced breast cancer therapy. The prognostic and/or predictive variables identified for the selection of systemic adjuvant therapy for breast cancer are age, race, tumour size, histologic tumour type, axillary nodal status, standard pathologic grade, and hormone receptor status. Polyphenols with anti-cancer properties have been the primary focus of public and medical attention in the effort to reduce cancer incidence. Flavonoid components, including phenethyl isothiocyanate (PIETC), quercetin (Qu), resveratrol (RES), and chlorogenic acid (CGA), which attract a lot of attention from the public, may have the potential to be used as an alternative or complementary medicine in the treatment of breast cancer because they have a wide range of biological attributes. The current trends in existing cancer therapy and prospects for cure are discussed in this review, along with the synergistic effect of polyphenols as a potential therapeutic agent in treating breast cancer. We summarise the evidence by comparing and contrasting diagnostic and treatment methods. Finally, the possibility of breast cancer prevention and more focused treatments was explored.

Keywords: Breast Cancer, Polyphenols, Breast Cancer Treatment, Synergistic, Flavonoid, and Chemotherapy

1. Introduction

Cancer remains a primary cause of death worldwide due to its persistent and lethal nature, making it challenging for many patients to find a cure. Surgical procedures, chemotherapy, radiation therapy, targeted therapy, and immunotherapy are currently utilised in cancer treatment. Moreover, these treatments are primarily effective only for patients with early-stage or sensitive cancers, limiting their overall impact on the ability to cure cancer (1). Among female cancer patients in the American women, breast cancer ranks as the second most common cause of mortality (2). In 2020, it was estimated that there were 47.8 cases of breast cancer per 100,000 females (3). Breast cancer now accounts for 12.5% of all cancer diagnoses in women, with an estimated 2.3 million new cases. This is followed by lung cancer at 12.2%, colorectal cancer at 10.7%, prostate cancer at 7.8%, and stomach cancer at 6%. By 2040, there will be 28.9 million new cases of cancer worldwide, a 47% increase from the current number (Global Cancer Observatory, 2020). Despite significant advances in early identification and a thorough understanding of breast cancer molecular biology, approximately 30% of patients with initial malignancies experience recurrence (4). Based on an analysis of existing literature and data sources, this article describes various types of cancer therapies currently available and their prognosis for cure.

2. Pathophysiology in Breast Cancer

Breast carcinoma is categorised based on histological markers that indicate the existence of specific receptors, including the estrogen receptor (ER), human epidermal growth factor receptor 2 (HER2), and progesterone receptor (PR). A lack of expression of any of these markers is referred to as triple-negative (5). Genetics and advancing age, with the incidence rising approximately twice every decade until menopause, when the rate of growth decreases significantly, are two factors that enhance the risk of getting breast cancer (6). After menopause, the age-incidence curve levels out in many countries.

Numerous studies have determined that a prior diagnosis of benign breast illness, a breast cancer genetic history, and the implementation of hormone replacement treatments are the strongest predictors of the disease (7). The incidence of breast cancer is found to be affected by numerous hormonal and reproductive variables, including age at menopause, years at menarche, height, and pregnancy rate. Sex hormones and early puberty milestones are believed to increase the risk of breast carcinogenesis. Early breast development (thelarche) is also emerging as a risk factor, with decreasing age at thelarche in the US and globally having a significant public health impact (8). Circulating levels of estrogens and androgens are linked to a higher risk of premenopausal breast tumours. The correlation between onset and end of the menstruation and the breast cancer risk may be more intricate than just prolonging a woman's reproductive years(9). Hormonal factors from the ovaries have a stronger effect on cancers that are positive for estrogen receptors than on those that are negative (10). Tumors in the lobules of the breast are more common than those in the ducts. Although the majority of breast cancer cases are due to genetic alterations in breast cells, there may also be a hereditary component to the disease (11). By identifying the genes responsible for hereditary breast cancer, it may be possible to detect early abnormalities and reduce the occurrence of breast cancer in the population (12).

3. Mammography

In 1956, mammography assessment was developed to detect early breast cancer. Randomized trials in the 1970s showed it reduced breast cancer incidence and mortality, especially in women aged 60 to 69. The goal of mammography programmes is to reduce mortality through earlier diagnosis and improved treatment outcomes (13), (14), and (15). Progressed tumours in the population of interest indicate the efficacy of screening and are not influenced by treatment. Despite varying definitions of disease severity, a meta-analysis of investigations found a substantial decline in the threat of late-stage diseases in older women over the age of 50 who participated in screening (RR 0.62, 95% CI 0.46–0.83). However, no benefit was noticed in women aged between 39 to 49 years (16). Screening decreased the occurrence of pT2-T4 lesions by 39% (66.3 vs. 108.6), increased pT2 by 28%, and increased pT3-T4 by 68%. The incidence rate ratio was 0.61 (95% CI: 0.57–0.66). The incidence of stage IIB increased by 35%, stage III by 43%, and stage IV by 73%, but stage II-IV illness was reduced by 28% (130.1 vs. 180.6; incidence rate ratio of 0.72, 95% CI 0.68–0.76). Additionally, screening led to a 50% rise in breast-conserving procedures and a 17% decrease in poorly differentiated carcinomas (17). Mammography screening lessened the chance of dying from breast cancer by 41% (related risk 0.59, 95% CI 0.51-0.68) and metastatic breast cancer by 25% (relative risk 0.75, 95% CI 0.66-0.84) within 10 years of diagnosis in a large population study of 549,091 women in 9 Swedish counties. In the United States, 44% of patients have stage I breast cancer, 30% have stage II, 9% have stage III, and 5% have stage IV. The 5-year survival rate for breast cancer ranges from 100% for stage I to 26% for stage IV (18).

4. Hormone replacement therapy (HRT)

Patients undergoing Hormone Replacement Therapy (HRT) and those who ceased between one and four years ago have a comparative risk of developing breast cancer that is 1.023 (1.011–1.036) times higher, respectively (19). The relative risk of breast cancer in non-users of HRT rises by a factor of 1.028 (1.021–1.034) for each year older at menopause, which is consistent with the effect of menopause postponement. Oestrogen use did not raise the risk of breast cancer, according to the majority of meta-analyses and observational studies from the 1990s (20). Treatments combining oestrogen and progesterone increased the risks related to dose and duration. The Women's Health Initiative (WHI) found that women who received conjugated oestrogen and medroxyprogesterone acetate had a noticeably higher risk of developing breast cancer than placebo users after 5.6 years (roughly 6-7 years) (21). Contrary to those who received a placebo, women receiving conjugated oestrogen had a lower risk of breast cancer. Current theories suggest that oestrogen may encourage non-cancerous occult tumour cells, and estrogen-progesterone therapy may intensify this effect. HRT has been linked to an increase in breast density as well as a decrease in the sensitivity and specificity of breast screening (22).

5. Chemotherapy

Studies have demonstrated the benefits of treatments like L-phenylalanine and mustard or the combination therapy of cyclophosphamide, methotrexate, and 5-fluorouracil as adjuvant chemotherapy for node-positive breast cancer since the 1970s (CMF). In the 1980s and 1990s, chemotherapeutic drugs such as Anthracyclines and Taxanes were discovered to be more efficient than CMF, and tamoxifen improved survival in patients who tested positive for the HR gene; AIs subsequently improved survival in postmenopausal women (23). In the 20s, targeted anti-HER2 therapies emerged as treatment options, revolutionising HER2-positive breast cancer management and prognosis. Genome expression profiling improved personalization of treatments, but patient selection remains crucial for effective and safe treatment (24).

TP53 mutations cause 30% of breast cancers. Its incidence is significantly linked to molecular tumour subtypes, which are seen in 26% of luminal tumours (17% luminal A and 41% luminal B), 50% of HER2-amplified tumours, 69% of molecular apocrine tumors, and 88% of basal-like carcinomas (25) (26). Neoadjuvant chemotherapy (NACT) is recommended to most locally advanced breast cancer patients including early stag illness, notably triple-negative or HER2-positive ones. The treatment's objective is to elicit a tumour response before surgery so that the breast can be saved (27, 28).

Table 1 US-FDA approved drugs for the treatment of breast cancer. (29)

Drug	breast cancer type	popular brand name(s) in the United States
Abraxane**	Recurrent / metastatic	Abraxane
Capecitabine	metastatic cancer that resists other chemotherapy	Xeloda
Cyclophosphamide	Advanced / metastatic	Cytoxan Revimmune Cycloblastin Neosar Endoxan
Docetaxel	metastatic cancer that has not responded to chemotherapy or node-positive malignancy resected by surgery	Taxotere
Doxorubicin	Surgery for node-positive malignancy	Caelyx Myocet Doxil
Epirubicin Hydrochloride	Surgery for node-positive malignancy	Ellence
Eribulin Mesylate	Cancer patients were treated with anthracyclines and taxanes.	Halaven
Fluorouracil Injection	Advanced/ metastatic stage	Efudex Adrucil
Gemcitabine Hydrochloride	Combined with paclitaxel in cancer in cases where prior other chemotherapy has failed to control cancer.	Gemzar
Goserelin Acetate	Advanced condition requiring palliative care	Zoladex
Ixabepilone	Locally advanced/metastatic cancer that has not responded to other chemotherapy.	Ixempra
Fluorouracil Injection	Advanced / metastatic stage	Efudex Adrucil
Methotrexate	Advanced /metastatic stage	Rheumatrex Trexall
Pamidronate Disodium	Bone metastatic stage	Aredia
Thiotepa	Advanced/ metastatic stage	Thioplex
Vinblastine Sulfate	Advanced/ metastatic stage	Alkaban-aq, Velban

About 15% of invasive breast cancers (BCs) are HER2 positive, characterised as HER2 gene amplification or an overexpression of the HER2 protein, and treatment with an anti-HER2 targeted medicine has been demonstrated to be effective in the treatment of these tumors. (30, 31), where Anti-HER2 medications have altered the disease's natural biology (32). Patients experiencing HER2-positive advanced breast carcinoma should receive HER2-targeted treatment with the exception of those with clinical congestive cardiac failure or a markedly decreased left ventricular ejection fraction, who should be examined on a individual basis (33). For first-line treatment, trastuzumab, pertuzumab, and taxane are suggested, as well as T-DM1 for second-line treatment. Other HER2-targeted treatment combinations or T-DM1 (if not previously provided) should be offered in the third-line scenario, as should pertuzumab if the patient has not previously received it. Chemotherapy should be given for at least 4 to 6 months or until a maximal response is achieved (34, 35).

5.1 *Chemotherapy Using Polyphenols*

Coffee beans contain chlorogenic acid (CGA). This polyphenol has an important function in cancer pathogenesis. To defend and scavenge against free radicals, CGA stimulates endogenous antioxidant mechanisms (36, 37). It promotes nuclear translocation of Nrf2 from the cells' cytoplasm, resulting in the activation of antioxidant gene sets that protect cells against harm. CGA supplementation enhances the management of oxidative damage and the formation of free radicals in advanced animal models of many chronic and metabolic illnesses (38).

Studies have demonstrated the possible effects of phenethylisothiocynate on gastric cancer (GC) cells, and the probable underlying mechanisms have also been investigated. The research revealed that PITC inhibited the cell viability of two GC cell lines and caused them to enter into cell cycle arrest and apoptosis. Treatment with PITC caused total glutathione depletion in GC cell lines, causing reactive oxygen species accumulation and resulting in DNA damage, which triggers the mitochondria-dependent and p53 signalling pathways to kill the cells. The study concluded that PITC may induce GC cell apoptosis via mitochondria-dependent apoptosis and DNA damage (39). Several studies have revealed the anti-inflammatory and anti-oxidant properties of Qu and its effect on proliferation, angiogenesis, and apoptosis (anti-tumour properties), which aid in breast cancer treatment (40). Research findings have also shown quercetin's chemopreventive and curative properties for ovarian cancer, which are discussed, as are some of the most current studies on the molecular pathways by which this natural chemical suppresses this disease (41). A tumour necrosis factor-related apoptosis inducing ligand (TRAIL) has been researched to have anticancer efficacy in various cancerous forms, especially ovarian cancer. The quercetin can reduce the effect of sensitization of ovarian cancer cells to TRAIL. The data from the study showed that quercetin increased the sensitivity of tumour cells to TRAIL, which in turn lowered the production of cell survival proteins, slowed tumour growth, and boosted pro-apoptotic proteins expressions especially caspase-3 (42).

6. Breast Conserving Therapy (BCT)

BCT is a procedure that involves removing the tumour surgically (lumpectomy) and administering adjuvant whole-breast radiation (WBI). The patient must be able to receive radiation treatment, the tumour must be removed with acceptable cosmetic results, and the breast must be suitable for follow-up to quickly detect local recurrence. The presence of dispersed suspicious or malignant-looking nodules, an ailment that cannot be surgically corrected to negative margins with an adequate cosmetic result, and the existence of contraindications to radiation delivery are all BCT contraindications that follow logically from these requirements (43). The phrase "no ink on the tumour" describes a negative margin. Wider clean margins are not advantageous for invasive breast cancer patients, and BCT does not require them (44). A study-level meta-analysis was used to carefully review the information on surgical margins in patients with early-stage invasive breast cancer receiving BCT (45). According to meta-analysis, negative margins are associated with a lower risk of local recurrence (LR); however, when follow-up duration is taken into account, a lower risk of LR is not significantly correlated with increasing the distance used to define negative margins (46).

7. Postmastectomy radiotherapy (PMRT)

Breast cancer patients diagnosed with positive axillary lymph nodes may benefit from postmastectomy radiation therapy (PMRT). However, there is considerable controversy surrounding the effeciency of radiation in pathological negative nodes (ypN0) after neoadjuvant chemotherapy. A study has been conducted to determine whether PMRT improves locoregional control and survival in these patients (47). According to the meta-analysis, PMRT may lower the local-regional recurrence after NAC for patients with ypN0, but it has no effect on survival outcomes; to confirm further findings, a prospective randomised clinical trial would be required. Patients with stage II or stage III breast cancer with pathologically negative lymph nodes, i.e., ypN0 were examined for PMRT effectiveness following neoadjuvant treatment. (48). Clinically, patients with YPN0 stage II-III breast cancer who received NAC responded differently to PMRT. For patients with clinical stage IIIB or IIIC disease, T3 or T4 tumours, or invasive breast tumours, PMRT following NAC was superior to NAC alone. The study identified clinically node-positive, stage II–III breast cancer patients who may benefit from PMRT after NAC in the absence of prospective trials (49). Zhang et al. used pathologic markers to determine whether postmastectomy radiation therapy after neoadjuvant chemotherapy (NACT) and total mastectomy (TM) benefits patients (PMRT). PMRT improves overall survival (OS) in NACT and TM-treated patients with ypT3–4, ypN2–3, or pathologic stages IIIA-IIIC breast cancer. PMRT increased loco regional recurrence-free survival in NACT and TM-treated breast cancer patients, including pathological complete response (pCR) (50).

8. Conclusion

Despite advances in the intervention, Breast Cancer is still the second-leading cause of death globally. Treatment for breast cancer is difficult and entails numerous clinical trials of cutting-edge treatments. While HER^{2+} BC receives anti-HER^2 therapy, HR^+ BC receives endocrine therapy. Treatments for BC have a long history of success and safety. Triple Negative Breast Cancer, the BC subtype with the lowest survival rate, is difficult to treat with targeted therapies. Because all molecular subtypes of BC are resistant, mTOR/PI3K/Akt pathway inhibitors may be used to treat it. In order to supplement BC treatments, this article recommends using natural compound nutrition as a dietary supplement, adjuvant, or complementary cancer medicine.

Conflict of Interests

The authors declare that there are no conflicts of interest.

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