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Review

Breast Cancer- In 21st Century Current Status and Future Perspective

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ABSTRACT

The most frequent cancer type in females in the world is breast cancer; with a lifetime risk of the order of 1/10.Breast cancer is the most common invasive cancer in females. It usually presents with a lump in the breast with or without other manifestations. The tumor is malignant (cancer) if the cells can grow into (invade) surrounding tissues or spread (metastasize) to distant areas of the body. Breast cancers can start from different parts of the breast. Our understanding of the molecular events relating to breast cancer biology and pathogenesis has greatly increased over the last decade. Diagnosis of breast cancer depends on physical examination, mammographic findings and biopsy results. Treatment of breast cancer depends on the stage of the disease. Lines of treatment include mainly surgical removal of the tumor followed by radiotherapy or chemotherapy. Second lines including immunotherapy and other therapy and alternative medicine may represent a hope for breast cancer patients.

Keyworld- breast cancer, lump, molecular events, biology and pathogenesis, radiotherapy.

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INTRODUCTION

Breast cancer is the most common cancer form in women; in the countries with highest incidence rates, the lifetime risk of developing breast cancer is over 10%. Although breast cancer has a better prognosis than many other cancer forms, with 10-year relative survival rates of up to 80% in some countries, the burden of breast cancer remains considerable. As a result of improved treatments, more and more patients are cured, while others will live on with stable disease for a long time. However, much remains to be done and can be done in a combined approach to increase the early detection and treatment of breast cancer and optimise care organisations to further improve outcomes [1]. For example, survival still differs considerably between countries that appear to have comparable economic and human resources dedicated to healthcare. This highlights a key discrepancy in cancer care and calls for the further assessment of best practices in prevention and treatment and the adaption of such across countries. Although survival is the most important measure of outcomes in breast cancer, quality of life should also be included as an important marker, as the care the patient experiences impacts greatly on their psychological and physical well being as well as on their socio-economic situation. Over the last 30 years, major paradigm shifts in the treatment and organisation of breast cancer care include: the implementation of programmes for early detection using mammography; the introduction of adjuvant treatment such as endocrine therapy, chemotherapy and adjuvant radiotherapy following surgical treatment in breast cancer; and the implementation of multidisciplinary care. The change in surgical procedures from mastectomy (total removal of the breast) to more localised excision of tumours complemented by sentenial node biopsy, which makes it possible to fine-tune further treatment, is an important example of how quality of life has been improved without

compromising survival. In recent years, targeted biological therapies such as trastuzumab, for the treatment of early as well as metastatic breast cancer, have resulted in further improvement of outcomes [1].

TYPES OF BREAST CANCER

Breast cancer is generally considered to be a highly heterogeneous cancer type [2], encompassing distinct phenotypic and morphological profiles, and thus possess very different clinical behaviors [3]. Clinically, breast cancers are characterized into three basic types based on their immunohistochemical (IHC) properties (hormone status). They are hormone receptor-positive, HER2 positive (HER2+), and triple negative breast cancers. Hormone receptor-positive are the breast cancers with estrogen receptor-positive (ER+)/progesterone receptor-positive (PR+). Approximately 85% of all breast cancers are hormone receptor-positive. They can be treated with hormone therapies, including tamoxifen and the aromatase inhibitors, anastrozole (Arimidex), letrozole (Femara) or exemestane (Aromasin). Hormone receptorpositive breast cancers can be further divided into two subtypes: Luminal A and Luminal B. Luminal A tumors tend to be ER+ and/or PR+, and HER2-negative (HER2-). Luminal B tumors tend to be ER+ and/or PR+, and HER2+ (or HER2- with high Ki67). HER2+ refers to breast cancer that is human epidermal growth factor receptor 2 positive but hormone receptor-negative. About 20% of all breast cancers are HER2+. This type of breast cancer can be treated using anti-HER2 drugs, such as trastuzumab (Herceptin). Triple-negative breast cancers, also called basal-like subtype, refers to any breast cancer that does not express the genes for estrogen receptor, progesterone receptor or HER2 receptor. Triple-negative breast cancers account for around 15% of all breast cancer population. Since this type of breast cancer does not overexpresses receptors, targeting therapies are not helpful. Clinically, this type is treated with a combination of surgery, radiation therapy and chemotherapy. Other than these three major types, there are some minor molecular subtypes that are less characterized, such as luminal C subtype, normal breast-like subtype [4-6].

EPIDEMIOLOGY OF BREAST CANCER

Incidence and mortality Worldwide: Globally, over one million women are diagnosed with breast cancer every year. It is the most frequently diagnosed cancer in women1 and the leading cause of cancer death in women. Every year more than 500,000 women die from the disease [7, 8].

Lifetime risk of breast cancer On average one in eight women will develop breast cancer in their lifetime. This is double the risk of developing lung cancer, the second most common cancer in women [9].

Prognosis Cancer statistics often use an 'overall 5 year survival rate' to give a better idea of the longer term outlook for people with a particular cancer. It is almost impossible to predict how long an individual patient might live, but 5 year survival rates can give an approximate range. The 5 year survival rate describes on average the 'amount' of people that will be alive 5 years after diagnosis. The average 5 year survival rate for women with early stage breast cancer is 81%.However; on average only 35% of women with late or advanced stage breast cancer currently survive for 5 years [10].

RISK FACTORS FOR BREAST CANCER [11]

Genetic factors: Genetic factors are known to be involved in increasing the risk of a number of cancers, including breast cancer. A woman's inherited genetic profile impacts her risk of developing breast cancer. Approximately 5-10% of breast cancers are attributable to genetic factors. The most common breast cancer susceptibility genes are BRCA1, BRCA2, PTEN (Cowden syndrome), and TP53 (Li-Fraumeni syndrome). Research continues to explore additional susceptibility genes, as well as gene-environment interactions. Each child of a parent with a mutation has a 50% chance of inheriting the mutation. For persons with BRCA1 or BRCA2 mutations, the estimated risks of developing breast cancer by 70 years of age is about 55-65% (BRAC1) and 45-47% (BRAC2). BRCA1 and BRCA2 mutations can be inherited from either parent. Genetic mutations may vary by ethnic group, for example, studies of women in sub-Saharan Africa, Asia, and Latin America identified variable rates of BRCA1 and BRCA2 mutations ranging from 0.5-18% when testing moderate- to high-risk populations. Genetic testing requires both laboratory expertise and genetic counseling services, which are often not available in low-resource settings.

Family history of breast cancer: One's risk of developing breast cancer increases with the number of affected first-degree relatives. This is thought to be due to a combination of factors, both inherited (although not a specific gene) and environmental.

Personal history of breast cancer: For women with a personal history of breast cancer (DCIS or invasive breast cancer) there is an increased risk of developing a second breast cancer in either the same breast or the opposite breast (estimates suggest a 4% increase over 7.5 years).

Exposure to therapeutic ionizing radiation: Exposure to ionizing therapeutic radiation of the chest at a young age (highest risk if exposed at 10-14 years of age) increases one's risk; however, the risk of developing decreases dramatically if radiation is administered after age 40. For example, therapeutic radiation at a young age for treatment of Hodgkin lymphoma is associated with an increased risk of breast cancer. However, there are no data to suggest that current radiation therapy practices administered as part of breast cancer treatment, (i.e., radiation therapy after lumpectomy) increases the risk for developing a second breast cancer. Additionally, mammography and chest x-rays do not appear to increase breast cancer risk.

Hormonal and reproductive factors: Endogenous hormones (hormones produced within the body's cells), particularly estrogen exposure, play a role in breast cell growth and proliferation. Elevated or prolonged endogenous estrogen levels are associated with an increase risk of breast cancer in post-menopausal women. Known risk factors for breast cancer are associated with reproductive factors which extend natural exposure to hormones produced by the ovaries such as early onset of menstruation, late onset of menopause, later age of first pregnancy (i.e., over 30 years of age) and never having given birth. Laboratory evidence also suggests that higher levels of other endogenous hormones, (such as insulin and insulin-like growth factor (IGF), may play a role in breast cancer development.

Therapeutic or exogenous estrogen hormones: The use of prolonged hormone replacement therapy (HRT) after menopause has been associated with an increased risk of breast cancer. In a large randomized trial, women who took the combination of estrogen and progesterone for

more than 5 years after menopause had an increased risk of being diagnosed with breast cancer. It is now recommended that HRT should be used only for specific indications (such as significant menopausal symptoms) and the duration of treatment should be limited.

Age: The risk of breast cancer increases with age and in some high-resource settings in populations that have a long life expectancy the lifetime risk could be as high as 1 in 8 women. The impact of age on breast cancer incidence in LMICs is less well studied, but becomes increasingly important as life expectancy improves.

Weight (obesity): An association between obesity and breast cancer risk is thought to be at least partially related to the role of fat cells in contributing to levels of circulating hormones and other factors. Adiposity (fat cell volume) can affect circulating hormones as estrogen precursors are converted to estrogen in fat cells. Women's estrogen levels also vary based on their menopausal status, so the effect of obesity on breast cancer risk may depend on the menopausal status of the woman, with post-menopausal women being more affected than premenopausal women. Some experts suggest that up to 20% of breast cancer cases could be avoided by increasing physical activity and avoiding weight gain.

Alcohol consumption: Harmful use of alcohol is associated with an increased risk of breast cancer. Experts suggest that up to 14% of breast cancers could be avoided by substantially reducing or eliminating harmful use of alcohol.

PATHOGENESIS (HORMONE SENSITIVE) BREAST CANCER

Gene expression in breast carcinomas Two different types of estrogen receptors exist, alpha (α) and beta (β) (ERα and ERβ respectively). Various tissues express these receptors with breast, ovaries and the endometrium expressing ERα, while the kidneys, brain, lungs and several other organs expressing ERβ. The role of ERβ in carcinogenesis remains controversial whereas, a clear contribution of ERα protein has been established. Both ER subtypes carry a DNA binding domain and exist in the nucleus and the cytosol. When estrogen enters the cell, it binds the ER and the complex migrates into the nucleus and leads to the production of transcription proteins that induces changes in the cell. Therefore, due to estrogen's proliferative properties, its cellular stimulation can have negative consequences in patients expressing large quantities of these receptors intracellularly[12,13].

Role of estrogen in breast cancer progression and development Two major hypotheses attempt to explain the tumorigenic effects of estrogen: (i) genotoxic effects of estrogen metabolites via generation of radicals (initiator) and (ii) the hormonal properties of estrogen inducing proliferation of cancers as well as the premalignant cells (promoter) [12,13]..

Role of Human Epidermal Growth Factor Receptor 2 (HER2) HER2 belongs to the epidermal growth factor receptor (EGFR) family of proto-oncogenes and currently is not known to have a ligand. However, the protein has been shown to form clusters within the cell membranes in malignant breast tumours. Its mechanism of carcinogenesis remains largely unknown, but overexpression is associated with rapid tumour growth, shortened survival, increased risk of recurrence after surgery, and poor response to conventional chemotherapeutic agents [12, 13].

SIGNS AND SYMPTOMS OF BREAST CANCER

The most common symptom of breast cancer is a new lump or mass. A painless, hard mass that has irregular edges is more likely to be cancer, but breast cancers can be tender, soft, or rounded. They can even be painful. For this reason, it is important to have any new breast mass, lump, or breast change checked by a health care professional experienced in diagnosing breast diseases. Other possible symptoms of breast cancer include:

- Swelling of all or part of a breast (even if no distinct lump is felt)
- Skin irritation or dimpling (sometimes looking like an orange peel)
- Breast or nipple pain
- Nipple retraction (turning inward)
- Redness, scaliness, or thickening of the nipple or breast skin
- Nipple discharge (other than breast milk)

Sometimes a breast cancer can spread to lymph nodes under the arm or around the collar bone and cause a lump or swelling there, even before the original tumor in the breast is large enough to be felt. Swollen lymph nodes should also be checked by a doctor [14,15].

DIAGNOSIS OF BREAST CANCER

Physical examination of the breasts by a healthcare provider and mammography are considered as the primary tools for diagnois of breast cancer [16]. Fine needle aspiration and cytologycan also help to establish the diagnosis with a good degree of accuracy. Other types of biopsy include core biopsy or an excisional biopsy, in which the entire lump is removed. Imaging techniques such as ultrasound, computed tomography or magnetic resonance imaging are sufficient to give the physician accurate diagnosis and staging of the disease [17].

PREVENTION OF BREAST CANCER

Proper control of body weight, drinking less alcohol, physical exercises and breastfeeding are valuable measures for reduction of the risk of breast cancer. Also, dietary consumption of omega-3 polyunsaturated fatty acids and soya beans appears to reduce the risk [18]. The selective estrogen receptor modulators (such as tamoxifen) reduce the risk of breast cancer but increase the risk of thromboembolism and endometrial cancer. They are recommended only for prevention of breast cancer in women at high risk. The benefit of breast cancer reduction continues for at least five years after stopping these medications [19].

MANAGEMENT OF BREAST CANCER

Management of breast cancer depends on many factors including the stage of the cancer and the age of the patient. Breast cancer is usually treated with surgery, which may be followed by chemotherapy or radiation therapy, or both (Figure 1). Hormone receptor-positive cancers are often treated with hormone-blocking therapy over several years. Monoclonal antibodies or other immunomodulators may be given in advanced stages with distant metastasis [20].

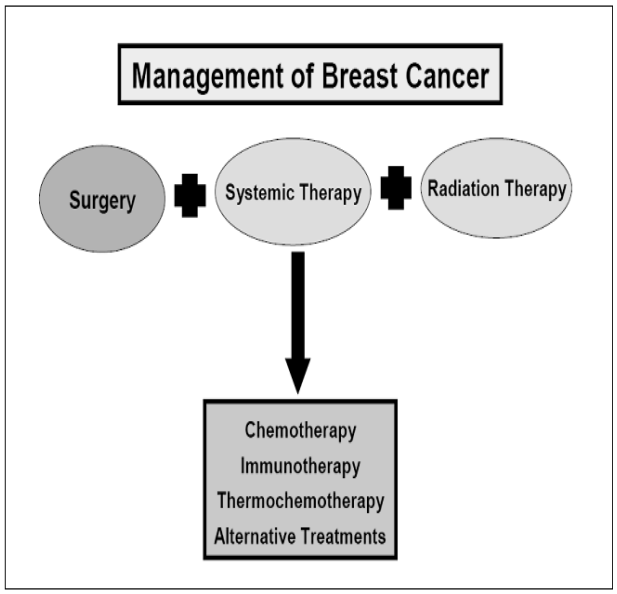

Figure 1: Lines of treatment of breast cancer

•***Surgery*** Depending on the stage and type of the tumor, just lumpectomy may be all that is necessary, or removal of larger amounts of breast tissue may be necessary. Surgical removal of the entire breast is called mastectomy [21]. A mastectomy involves removing all of the breast tissue, sometimes along with other nearby tissues. Before lumpectomy, a needle-localization of the lesion with placement of a guidewire may be performed. However, mastectomy may be the preferred treatment in multifocal cancer, breast previously treated with radiotherapy, large tumor relative to the size of the breast and if the patient has any disease of the connective tissue which may complicate radiotherapy. During the operation, the lymph nodes in the axilla are also considered for removal. If the removed tissue does not have clear margins, further removal of a part of the pectoralis major muscle may be needed [22].

•***Radiotherapy*** Radiation therapy is treatment with high-energy rays or particles that destroy cancer cells. This treatment may be employed to kill any cancer cells that remain in the breast, chest wall, or lymph node areas after breast-conserving surgery. Radiotherapy has gained an increased importance, and a recent meta-analysis revealed that radiotherapy as a complement to surgery decreased the risk of loco-regional relapse by two-thirds compared to surgery alone [23].External beam radiation is the most common type of radiation therapy for women with breast cancer. If breast-conservation surgery was performed, the entire breast receives radiation, and sometimes an extra boost of radiation is given to the area in the breast where the cancer was removed to prevent it from coming back in that area. The purpose of radiation is to reduce the chance of recurrence. Radiation therapy involves using high-energy X-rays or gamma rays that target a tumor or tumor site. This radiation is very effective in killing cancer cells that may remain after surgery or recur where the tumor was removed [24].

•***Chemotherapy*** Chemotherapy may be used before surgery, after surgery, or instead of surgery for inoperable cases. Patients with estrogen receptor positive tumors will receive hormonal therapy after chemotherapy is completed. Systemic chemotherapy is delivered through the bloodstream to reach cancer cells throughout the body. Chemotherapy for breast cancer may be given through an intravenous (IV) tube placed into a vein or as a pill or capsule that is swallowed (orally). Patients may have treatment once a week, once every 2 weeks (also called dose-dense chemotherapy), once every 3 weeks, or even once every 4 weeks. Common drugs for breast cancer include: Cisplatin (Platinol) Cyclophosphamide (Neosar) Docetaxel (Docefrez, Taxotere) Doxorubicin (Adriamycin) Epirubicin (Ellence) Eribulin (Halaven) Fluorouracil (5-FU, Adrucil) Gemcitabin(Gemzar) Ixabepilone (Ixempra)Methotrexate (multiple brand names) Paclitaxel (Taxol)Pegylated liposomal doxorubicin (Doxil)Protein-bound paclitaxel (Abraxane)Vinorelbine (Navelbine). The side effects of chemotherapy depend on the individual, the drug(s), the schedule, and the dose used. In general, side effects include fatigue, risk of infection, nausea and vomiting, hair loss, loss of appetite, and diarrhea. These side effects can often be prevented or managed during treatment, and they usually go away once treatment has finished. Rarely, long-term side effects may occur, such as heart or nerve damage or secondary cancers [25].

•***Hormonal therapy*** For women with ER- or PR-positive breast cancer, hormonal therapy, also called endocrine therapy, is typically recommended. Because these types of tumors use hormones to fuel their growth, blocking the hormones can help prevent recurrence and death, either by itself or following adjuvant or neoadjuvant chemotherapy. Hormonal therapy is also effective as a treatment for metastatic breast cancer, shrinking the cancer and improving cancer-related symptoms [26].

Tamoxifen (Nolvadex, Soltamox) Tamoxifen blocks estrogen from attaching to breast cancer cells. It is effective at reducing the risk of recurrence in the breast that had cancer, the risk of developing cancer in the other breast, and the risk of distant recurrence. It is also approved to reduce the risk of breast cancer in women at high risk for developing the disease and for reducing local recurrence for women with DCIS who had a lumpectomy The side effects of tamoxifen include hot flashes; vaginal dryness, discharge, or bleeding. Very rare risks include a cancer of the lining of the uterus, cataracts, and blood clots. However, tamoxifen improves bone health and cholesterol levels and can be effective for both premenopausal and postmenopausal women [26].

Aromatase inhibitors (AIs) Drugs such as anastrozole (Arimidex), exemestane (Aromasin), and letrozole (Femara) decrease the amount of estrogen made by tissues other than the ovaries in postmenopausal women. Research shows that all 3 AI drugs work equally well and have similar side effects, which may include muscle and joint stiffness and pain, hot flashes, vaginal dryness, an increased risk of osteoporosis and broken bones, and higher cholesterol levels. Women who have not yet gone through menopause should not take AIs because they do not block the effects of estrogen made by the ovaries. Often, doctors will monitor blood estrogen levels in women whose periods have recently stopped, or whose periods stop with chemotherapy, to make sure the ovaries are no longer producing this hormone [26].

Ovarian suppression Stopping the ovaries from making estrogen is one of the oldest hormonal treatments for hormone receptor-positive breast cancer and for premenopausal women with metastatic breast cancer. Medications called gonadotropin or luteinizing releasing hormone (GnRH or LHRH) analogues stop the ovaries from making estrogen, causing temporary menopause. Goserelin (Zoladex) and leuprolide (Lupron) are drugs given by

injection under the skin that stop the ovaries from making estrogen for 1 to 3 months. Most commonly, these drugs are given with tamoxifen or AIs as part of adjuvant therapy for breast cancer. Less commonly, they are given alone. Surgical removal of the ovaries, called an oophorectomy, may also be considered for some patients; however, the hormonal effects of this surgery are permanent [26].

•***Targeted therapy*** Targeted therapy is a type of drug treatment that targets the cancer's specific genes, proteins, or the tissue environment that contributes to cancer growth and survival. This type of treatment blocks the growth and spread of cancer cells while limiting damage to healthy cells.Research studies show that not all breast tumors have the same targets. To find the most effective treatment, your doctor may run specialized tests to identify genes, proteins, and other factors specific to your tumor. The first targeted therapies used to treat breast cancer were hormonal therapies. Then HER2 targeted therapies were approved to treat HER2-positive breast cancer [27].

HER2 Targeted Therapy If your cancer is HER2 positive, your doctor may recommend medications that only affect HER2-positive cancer cells. These anti-HER2 treatments block HER2 to stop the growth of cancer cells.

Trastuzumab (Herceptin) Trastuzumab is approved for the treatment of HER2-positive breast cancer. Currently, patients with stage I to stage III breast cancer typically receive a trastuzumab-based regimen, often including a combination of trastuzumab with chemotherapy, followed by completion of one year of adjuvant trastuzumab. Patients receiving trastuzumab have a small (2% to 5%) risk of heart problems, and this risk is increased if a patient has other risk factors for heart disease. These heart problems may go away and can be treatable with medication. Trastuzumab is also an important part of treatment for metastatic HER2-positive breast cancer [28].

Pertuzumab (Perjeta) Pertuzumab is approved as part of neoadjuvant treatment for breast cancer in combination with trastuzumab and chemotherapy. It is also used in combination with trastuzumab and chemotherapy for metastatic HER2-positive breast cancer [29].

Ado-trastuzumab emtansine or T-DM1 (Kadcyla) T-DM1 is a combination of trastuzumab linked to a type of chemotherapy. This allows the drug to deliver chemotherapy into the cancer cell while reducing the chemotherapy received by healthy cells. T-DM1 is approved to treat metastatic breast cancer [30].

Lapatinib (Tykerb) Lapatinib is approved for the treatment of metastatic HER2positive breast cancer. It may be given in combination with capecitabine or with letrozole [30].

Neratinib (Nerlynx) This oral drug is approved as a treatment for higher-risk HER2-positive, early-stage breast cancer. It is taken for a year, starting after patients have finished 1 year of trastuzumab [31].

•***Immunotherapy*** The immune system can fightmany types of tumors including breast cancer.A new clinical trial is designed to use oncofetal antigen (OFA) to recruit the patient's ownimmune system to target and attack the cancer cells to improve patient survival and quality of life. Each patient will receive three monthly injections of the patient's own dendritic cells that have been sensitized to OFA. It is anticipated that once the sensitized cells are injected back into the patient, the patient's T-cells will locate the OFA found on the patient's cancer cells, thereby generating an immune response with killing of the cancer cells and preventing further spread of the disease. Stimuvax is a therapeutic cancer vaccine designed to induce an immune response to cancer cells that express MUC1, a glycoprotein antigen over-expressed on most cancers. Stimuvax is thought to work by stimulating the body's immune system to identify and destroy cancer cells expressing MUC1[32].

•***Thermochemotherapy*** Medifocus heat treatment added to chemotherapy increased the median tumor shrinkage in the thermochemotherapy arm to 88.4%, while for chemotherapy alone the median tumor shrinkage was 58.8%. For the thermo-chemotherapy treatment arm, almost 80% of breast tumors had a tumor volume reduction of 80% or more, compared to only 20% for the chemotherapy alone [32].

•***Alternative and Adjunctive Treatments*** Recent studies have begun treating women suffering from breast cancer with a procedure known as cryoablation. The treatment freezes, than defrosts tumors using small needles so that only the harmful tissue is damaged and ultimately dies. The advantage of this technique includes alternative to surgery, limiting hospital visits and reducing scarring [32]. Also, traditional herbal medicine was used as adjunctive therapy for treatment of breast cancer. They were proven, in combination with conventional therapy, to improve quality of life and decrease the number of hot flashes per day [33]. Other lines of alternative therapy include group support therapy, cognitive behavioral therapy, cognitive existential group therapy, a combination of muscle relaxation training and guided imagery, thymus extract, transfer factor and melatonin. Encouraging but not fully convincing results were found for melatonin [34].

•***Medicinal Plants in Breast Cancer Therapy*** Among Complementary and alternative medicines, herbal medicine is the most commonly used group of treatment. Herbal treatment is the oldest used system of medicine in the world with more than 2000 years history. Other names used for herbal therapy are phytomedicine, phyto-therapy or botanical medicine. phytoconstituents resulting from the herbs such as Vinca rosea, Taxus species, Allium sativum, Aloe vera, Angelica sinensis, Astragals membranaceus, Glycine max, Glycyrrhiza glabra, Hordeum vulgare, Hydrocotyle asiatica, Medicago sativa, Morinda citrifolia, Panax pseudoginseng, Saussurea lappa, Taxus wallichiana, Tinospora cordifolia, Viscum album, Withania somnifera, Zingiber officinale etc. have been used in numerous preparations to improve function of the body's immune cells that stimulates production of cytokines including interleukin, interferon, tumor necrosis factor as well as colony stimulating factor. These preparations assist the body to battle cancer more efficiently and also decrease the harmful side effects of chemotherapy and radiotherapy [35].

CONCLUSION

Breast cancer represents one of the most common tumors in females worldwide. Its early diagnosis is the first step for effective treatment. Treatment regimen should consist of combination therapy to achieve high cure rate and decrease the risk of recurrence.

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