BREAST CANCER: EPIDEMIOLOGY, DIAGNOSE AND MANAGEMENT GUIDELINES
(Review)

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ABSTRACT: Breast cancer is the commonest cancer among females and it is a leading cause of death all over the world. This disease is characterized by rapid and uncontrolled proliferation of abnormal cells which may mass together to form a growth or tumor, or spread throughout the body, initiating abnormal growth at another site. Breast cancer is a worldwide problem and mostly diagnosed at advanced stages. The diagnosis of breast cancer is confirmed by biopsy of the lump. Once the diagnosis is made, further tests are advised to determine if cancer has spread afar from breast and which treatments it may respond. A number of treatments may be used in those who have been diagnosed with cancer, including surgery, radiation therapy, chemotherapy and targeted therapy. The medications tamoxifen or raloxifene may be used to treat and prevent breast cancer. We have tried to discuss the epidemiology, diagnosis and treatment of breast cancer. Herein, we suggest evidence-based medicine for the treatment of breast cancer and diagnostic techniques in special conditions on the basis of expert opinion and literature review.

Key words: Breast cancer, incidence, chemotherapy, epidemiology, medicinal plants.

INTRODUCTION

Breast cancer is the most common cancer among female and contributes 11% among all types of cancer diagnosed worldwide annually. Breast cancer mostly originates from milking ducts or lobules, which supply the milk towards the ducts. That’s why on the basis of origination, breast cancers may be ductal or lobular carcinomas. Its chief risk factors are obesity, hormone therapy and alcohol drinking [1]. Inherited mutations in the BRCA1 and BRCA2 genes are also the commonest cause of breast cancer. About 5-10% cases of breast cancers are due to mutation of genes. In general, when cells not further required for body undergo apoptosis after completion of their life cycle. Before apoptosis, they are protected by PI3K/ AKT pathway and RAS/MEK/ERK pathway. In some condition genes linked with these pathways getting mutated and cause permanent opening of these pathways causing the continuous, uncontrolled proliferation of cells and prevents cell suicide after completion of their life span. Usually PTEN protein involves in turning off the PI3K/AKT pathway at the time of cell apoptosis. In some cases PTEN protein become mutated which leads to uncontrolled proliferation of tumor cells [2].

Epidemiology

Breast cancer is the most common tumor all over the world among women. With the exception of Japan, there is large the geographical variation in its incidence; the incidence rate is highest in most developing countries. In the world, about half of the incident cases occur in Europe and North America. Since the 1970s the incidence of breast cancer has been increasing. A Westernized lifestyle, giving birth at an older age and fewer children are some of the causes for the increasing incidence of breast cancer worldwide [3]. Breast cancer is more common in single women than in married women [4]. Epidemiological investigations have also suggested that those women who have many children run a lower risk of breast cancer than those women who have fewer children. Incidence of breast cancer is predicted to increase to 85 per 100,000 women by 2021 [5]. In 2012, 1.67 million new cases of breast cancer were diagnosed that is 25% of all cancers among women. In Poland, seventeen percent of disease cases occur due to cancer and 14 % deaths due to cancerous changes. According to the data, 145.2 women in Belgium and 66.3 in Poland between 100,000 suffer from breast cancer [6]. Fifth most common cause of cancer death is breast cancer. Incidence of breast cancer is 10.04% among all cancer and, most commonly occurs in 40-50 aged women. Incidence of breast cancer in the United States is one out of eight women and In Asia one woman out of 35 suffers from breast cancer. In Iran, the ratio is 10 cases in 100,000 population and in addition, 7000 new cases reported annually [7]. Worldwide death due to breast cancer calculated in 2004 was 519000 [8]. In the United States, near about 1,208,000 breast cancer cases are reported per year and some 538000 people die from previous manifestations of the disease condition, representing about one fifth of total annual deaths from all causes. Association of clinico pathological characteristic and breast cancer subtypes has been determined in Iranian women [9]. Memon et al reported that the main reason of late presentation in Pakistani women is lack of awareness and 39% patients ignore breast symptoms in early stage [10]. Mean age of breast cancer in Iranian women is 48 years [11]. Prevalence of breast cancer is increasing in Pakistan [12]. Breast cancer is found mostly in highly populated areas of South Asian developing countries [13]. Breast cancer mostly occurs in obese women [14]. Depression is most commonly found in women with breast cancer [15]. Quality of life of breast cancer patients is badly affected and the main reason of lower quality of life includes anxiety, psychological stress, sexual problems, fear of recurrence, pain, fear of loss of fertility, impaired physical function, fatigue, sleep dysfunction and fear of loss of fertility [16]. Over 50 clinically approved antiproliferative anticancer drugs are marketed in the United states, and some 12% of all cancers are regarded as curable [17]. Yang et al, stated that new cases of breast cancer in China were 168,013 in 2005 and 121,269 in 2000 [18]. Presence of certain kinds of benign tumors in breast increases the risk of malignancy. The ovaries stop producing the female hormones once the menopause sets in, but in obese women the fatty tissue can provide the estrogen as it is capable of producing it. This
increase in hormone production seems to increase the risk of breast cancer in obese post menopausal women. In allopathic, cancer treatments may include: chemotherapy, radiation therapy, lumpectomy; mastectomy and hormonal therapy (Tamoxifen, Aromasin).

The adverse side effects of the breast cancer treatment are the motivating factor to find alternative methods. The use of medicinal plants for therapeutic purpose is considered a natural alternative, because some plants contain properties that naturally have the ability to treat breast cancer. Careful precautions and considerations are taken when studying the different plants reported to treat breast cancer. Vitamin D and lack of sun exposure is also considered as a cause of breast cancer [19]. Some examples of the medicinal plants that may use for breast cancer treatment are discussed.

Cruciferous vegetables reduce risk of carcinoma [20]. Sea weed has cytotoxic activity [21]. Some adverse effects are still expected, and it is essential that any patient interested in exploring the botanical treatment seeks the advice of a licensed medical professional [22]. Herbal medicine is an integral part of the development of modern civilization. The compounds synthesized by plants are of plant processes. It is quite interesting that our predecessors not only had succeeded to understand most of the plant processes, but also successfully correlated them with human health [23].

**Rate of preventing of breast cancer**

Preventability measures illustrate that about 22% of cases of Brazilian breast cancer cases can be prevented by not taking alcohol, being physically active and maintaining healthy weight. The Incidence rate is highest in Belgium, followed by Denmark and France. Some more extent of breast cancer was diagnosed in less developed countries (53%). Northern America and Oceania have the highest incidence of breast cancer; and the lowest incidence is in Asia and Africa [24].

### Table 1: Preventability estimates of breast cancer

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country</th>
<th>Age-Standardized Rate per 100,000 (World)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Belgium</td>
<td>111.9</td>
</tr>
<tr>
<td>2.</td>
<td>Denmark</td>
<td>105.0</td>
</tr>
<tr>
<td>3.</td>
<td>France (metropolitan)</td>
<td>104.5</td>
</tr>
<tr>
<td>4.</td>
<td>The Netherlands</td>
<td>99.0</td>
</tr>
<tr>
<td>5.</td>
<td>Bahamas</td>
<td>98.9</td>
</tr>
<tr>
<td>6.</td>
<td>Iceland</td>
<td>96.3</td>
</tr>
<tr>
<td>7.</td>
<td>United Kingdom</td>
<td>95.0</td>
</tr>
<tr>
<td>8.</td>
<td>Barbados</td>
<td>94.7</td>
</tr>
<tr>
<td>9.</td>
<td>United States of America</td>
<td>92.9</td>
</tr>
<tr>
<td>10.</td>
<td>Ireland</td>
<td>92.3</td>
</tr>
<tr>
<td>11.</td>
<td>French Polynesia</td>
<td>92.2</td>
</tr>
<tr>
<td>12.</td>
<td>Germany</td>
<td>91.6</td>
</tr>
<tr>
<td>13.</td>
<td>Italy</td>
<td>91.3</td>
</tr>
<tr>
<td>14.</td>
<td>Finland</td>
<td>89.4</td>
</tr>
<tr>
<td>15.</td>
<td>Luxembourg</td>
<td>89.1</td>
</tr>
<tr>
<td>16.</td>
<td>New Caledonia</td>
<td>87.6</td>
</tr>
<tr>
<td>17.</td>
<td>Australia</td>
<td>86.0</td>
</tr>
<tr>
<td>18.</td>
<td>Malta</td>
<td>85.9</td>
</tr>
<tr>
<td>19.</td>
<td>New Zealand</td>
<td>85.0</td>
</tr>
<tr>
<td>20.</td>
<td>Switzerland</td>
<td>83.1</td>
</tr>
</tbody>
</table>

### Table 2: Breast cancer survivors

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country</th>
<th>Number of women still alive five years after a breast cancer diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Belgium</td>
<td>41,418</td>
</tr>
<tr>
<td>2.</td>
<td>Denmark</td>
<td>20,714</td>
</tr>
<tr>
<td>3.</td>
<td>France (metropolitan)</td>
<td>230,385</td>
</tr>
<tr>
<td>4.</td>
<td>The Netherlands</td>
<td>57,493</td>
</tr>
<tr>
<td>5.</td>
<td>Finland</td>
<td>18,722</td>
</tr>
<tr>
<td>6.</td>
<td>Italy</td>
<td>209,048</td>
</tr>
<tr>
<td>7.</td>
<td>Germany</td>
<td>279,045</td>
</tr>
<tr>
<td>8.</td>
<td>United Kingdom</td>
<td>200,286</td>
</tr>
<tr>
<td>9.</td>
<td>United States of America</td>
<td>970,693</td>
</tr>
<tr>
<td>10.</td>
<td>Iceland</td>
<td>966</td>
</tr>
<tr>
<td>11.</td>
<td>Luxembourg</td>
<td>1,588</td>
</tr>
<tr>
<td>12.</td>
<td>Switzerland</td>
<td>23,750</td>
</tr>
<tr>
<td>13.</td>
<td>Sweden</td>
<td>27,428</td>
</tr>
<tr>
<td>14.</td>
<td>Malta</td>
<td>1,233</td>
</tr>
<tr>
<td>15.</td>
<td>Canada</td>
<td>98,091</td>
</tr>
<tr>
<td>16.</td>
<td>Barbados</td>
<td>754</td>
</tr>
<tr>
<td>17.</td>
<td>Australia</td>
<td>59,584</td>
</tr>
<tr>
<td>18.</td>
<td>New Zealand</td>
<td>11,557</td>
</tr>
<tr>
<td>19.</td>
<td>Ireland</td>
<td>11,316</td>
</tr>
<tr>
<td>20.</td>
<td>Norway</td>
<td>11,926</td>
</tr>
</tbody>
</table>

Jan.-Feb
Rate of breast cancer survivors

The statistics of 2012 show Belgium has the highest percentage of breast cancer survivors still alive five years after their diagnosis. After Belgium the highest fraction is in Denmark and France. There were approximately 3.2 million breast cancer women who had survived breast cancer for at least 5 years, in the more developed countries; the survival rates for less developed countries was 3.0 million. The utmost incidence of survivors still living five years after their breast cancer diagnosis was in Northern America and Europe; and the lowest ratio was in the Africa and Asia [24].

Guidelines for the management of breast cancer

The usual consideration of a doubtful breast cancer is Triple Assessment i.e. clinical examination, radiological investigations and histological findings of biopsies of suspicious abnormalities found on the physical examination or from radiology [25]. Women are guided for self examination of breast cancer. Women can find abnormalities in size and shape of breast on self examination [26]. Alipour et al conducted a study to investigate the SMS based and paper based paper learner’s satisfaction and learning effect. Gynecologists gave printed materials and text messages regarding the facts of breast cancer and breast cancer tests. Doctors found higher motivation and better effects in the SMS group than the printed material group [27]. Sreeedharian et al conducted a study in United Arab States hospitals. Self administered structured questionnaire was used to investigate practices of self examination and knowledge. Satisfactory results were found from this study [28]. Ozkan et al investigated the level of knowledge regarding self examination of breast cancer among 113 midwifery and nursing students [29]. These researchers showed that continuous education program about breast cancer can raise the awareness among the population. The diagnosis of the breast cancer is based on the clinical findings, radiological studies and pathological examinations. Clinical examination includes bimanual palpation of the breasts and the regional lymph nodes. Radiological examinations include bilateral mammography and ultrasound. Ultrasound breast imaging shows the size and position of the tumor, whether it is filled with fluid or is solid and needs to be biopsied to rule out cancer. This examination is quickly becoming a routine procedure for diagnosing lumps in young women [30]. Porika et al stated that tumor markers must be measured in all stages of breast cancer, including metastasis, treatment and diagnosis [31]. This measuring helps in finding lumps in dense tissue. The image can also be easily stored and transmitted to another radiologist for second view [32]. Tarhan et al., stated mammography may give false negative and false positive results in patients with dense breast tissues [33]. Kanaga et al stated that the practice of mammography is 19% in Malaysian women as compared to other studies which was 19% . Lack of health insurance coverage, low income and embarrassment were the main barriers to mammography as mentioned by earlier studies [34]. Magnetic resonance imaging (MRI) of the breast is usually not done routinely, but may be considered in cases of dense breast tissue, in cases of familial breast cancer with BRCA mutations, or where multiple tumor foci are doubtful. Pathological diagnosis is based on core needle biopsy. A core needle biopsy or fine needle aspiration biopsy should be done before the surgical operation. Final pathological diagnosis is done according to World Health Organization (WHO) classification [35]. When the diagnosis of breast cancer completed, then each case is individually discussed at multidisciplinary team (MDT) meeting. This includes the surgeons, radiologists, pathologists, radiation oncologists and medical oncologists to make sure the better line of treatment for each patient.

A pathological diagnosis is made by core needle or fine needle biopsy before any surgical operation. Final the pathological diagnosis must be made by observing all tissue removed such as axillary nodal status, total number of nodes, capsular infiltration and the level of nodes affected. Estrogen receptor (ER) and progesterone receptor (PR) status is essential, and determination of HER2 receptor status must be considered [25].

Clinical staging of Breast Cancer

Tumor, nodes, metastasis (TNM) staging system

The tumor staging system (TNM) help in evaluating the distribution of disease give guide line for the treatment suggestions and provide estimates of patient prognosis. The TNM staging system classification is given below.

Primary tumor (T)

T0 No confirmation of primary tumor
Tis Carcinoma in situ: ductal (DCIS) or lobular (LCIS) carcinoma, or Paget’s disease of the nipple with no tumor
T1 Tumor is 2 cm or less in greatest dimension
T2 Tumor greater than 2 cm, but not more than 5 cm in greatest dimension
T3 Tumor greater than 5 cm in greatest dimension
T4 Tumor of any size with direct extension to chest wall or skin

Regional lymph nodes (N)

N0 Regional lymph nodes cannot be evaluated.
N1 Metastasis to movable ipsilateral axillary lymph node
N2 a. Metastasis to ipsilateral axillary lymph node fixed to one another or matted to other structures A Clinically-apparent ipsilateral internal mammary lymph node in the absence of clinically-evident axillary lymph node metastasis.
N3 a. Metastasis to ipsilateral infraclavicular lymph node
b. Clinically-apparent ipsilateral internal mammary lymph node in the presence of clinically-evident axillary lymph node metastasis
c. Metastasis to ipsilateral supraclavicular lymph node with or without axillary or internal mammary lymph node involvement.

Pathological classification

pNx Regional lymph nodes cannot be assessed.
pNO No regional lymph node metastasis.
pN1 a. Metastasis to 1 to 3 axillary lymph nodes

Jan.-Feb
b. Metastasis to internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent

c. Metastasis to both a and b.

pN2

a. Metastasis to 4 to 9 axillary lymph nodes

b. Metastasis to clinically-apparent internal mammary lymph node in the absence of axillary lymph node metastasis.

c. Metastasis to ipsilateral supraclavicular lymph node.

Stage grouping

Stage 0: Tis, N0, M0

Stage I: T1, N0, M0

Stage IIa: T0, N1, M0 T1, N1, M0 T2, N0, M0

Stage IIb: T2, N1, M0 T3, N0, M0

Stage IIIa: T0, N2, M0 T1, N2, M0 T2, N2, M0 T3, N1, M0 T3, N2, M0

Stage IIIb: T4, N0, M0 T4, N1, M0 T4, N2, M0

Stage IIIc: any T, N3 Stage IV: any T, any N, M1 (WHO 2006)

Prognostic Indicators In Breast Cancer

Factors commonly associated with a less favourable prognosis are:

a. increasing tumour size

b. higher grade

c. the presence and number of lymph node metastases

Factors associated with less favourable prognosis among node negative disease are:

a. increasing tumour size

b. increasing histological grade

c. oestrogen-receptor negative

d. progesterone-receptor negative [25].

Treatment strategies

Breast cancer treatment takes different approaches depending on the type and stage of disease. Surgery is suggested when tumor is localized, followed by chemotherapy, radiotherapy and, for ER-positive tumors, adjuvant hormonal therapy (with tamoxifen or an aromatase inhibitor). Management of breast cancer is based on national and international guidelines and it is undertaken by a multidisciplinary team. Patients are roughly divided to high risk and low risk cases according to clinical criteria (age, type of cancer, size, presence or absence of metastasis). Each risk category has different policies for therapy. Treatment strategies include radiation therapy, surgery, chemotherapy, hormone therapy, and immune therapy [26].

Surgery

The common surgical options are mastectomy or breast conserving surgery followed by the radiation therapy [36]. Mastectomy is advised for patients with tumor size (>5cm in diameter), tumor multifocality, previous radiation to the breast, in setting of patient preference and in the infrequent setting of pregnancy-related breast cancer [36].

The surgeon must ascertain that the tissue removed during operation has margins clear of cancer. This indicates that cancer has been completely removed. If the excised tissue does not show clear margins, further operations may be necessary to remove more tissue. For this reason, sometimes removal of part of the pectoralis major muscle requires, which is main muscle of the anterior chest wall. During operation axillary lymph nodes are also considered for removal. In past, 10 to 40 axillary lymph nodes were removed during surgical operation surgical operations but this had the unfortunate side effect of causing lymphedema of the arm on the same side, as the removal of many lymph nodes affected lymphatic drainage. Now recently, the technique of sentinel lymph node dissection has become well fame, as it requires the removal of only few lymph nodes, resulting in lesser side effects [37].

Radiation therapy

Radiation therapy is usually advised for women receiving breast conservation surgery and in the postmastectomy women with a high possibility of local recurrence. Radiation therapy involves high-energy X-rays or gamma rays, are used that are effective in killing cancer cells. Radiation therapy can be of two types: external beam radiotherapy or internal beam radiotherapy (brachytherapy). In case of external beam radiotherapy, X-rays are administer from outside the body, whereas in case of brachytherapy the precise placement of radiation source(s) apply directly at the treatment site. Radiation therapy for breast cancer is generally carry out after surgery and is an integral part of breast-conserving therapy. Radiation therapy eradicates the microscopic cancer cells that may stay behind near the area where the tumor was surgically excised. The dose of radiation adjusted strong enough to ensure the suppression of the cancer cells. Radiation affects the normal cells and the cancer cells alike, causing a little damage to the normal tissue present around target site. Healthy tissues can restore themselves, while cancer cells do not repair themselves as like normal cells. External beam radiotherapy is usually given for a period of five days to seven weeks. Each therapy takes about 15 minutes. Currently, ‘accelerated partial breast irradiation’ (APBI), uses brachytherapy to give the radiation for a short duration of time. APBI induces radiation to only region surrounding the primary tumor and can normally be completed over the course of one week [38].

An exact approximation of risks associated with radiation therapy is difficult to establish for current patients because reported side effects often reflect treatment strategies that have now been improved and updated. Generally, side effects from radiation therapy are mild and well tolerated. Common temporary side effects may include skin hyper pigmentation or erythema and fatigue [39]. Studies using current radiation therapy techniques have not possessed an increased risk of cardiac disease in women treated with radiation therapy alone or in combination with standard dose doxorubicin; however, follow-up on these trials is still limited [40]. The principal advantage of adjuvant radiotherapy is a significant reduction in local recurrence rates. The 10-year probability of local recurrence is reported at 8.8% for women receiving...
radiotherapy and 27.2% for those who receive no radiotherapy. A considerable impact of radiotherapy on mortality has been more difficult to explicate in the elderly population. Meta-analysis study suggest an absolute mortality advantage at 20 years of 0.8 to 2.3% based on recurrence risk for women aged 60 to 69 years who receive radiation therapy [41]

**Systemic therapy**

Medicines are used in the systemic therapy to eradicate cancer cells throughout the body. Systemic treatments include hormonal therapy, chemotherapy and immune therapy.

**Hormonal Therapy**

National Institutes of Health in 2000 consensus statement propose that “adjuvant hormonal therapy should be recommended to women, whose breast tumors contain hormone receptor protein, without considering the age of woman, menopausal status, axillary lymph node involvement, or the tumor size.” Presently, tamoxifen is the most frequently used hormonal therapy. Adjuvant hormonal therapy is not presently advised for ER negative breast cancer. These recommendations are in fact the results from the clinical trials on Early Breast Cancer. Collaborative Group, give suggestion, that five years of adjuvant tamoxifen therapy ER women results in a 50% reduction in recurrence rate and 28% decrease in the mortality at 10 years. In the ER, node positive cases 10.9% survival for 10-years was observed after five years of tamoxifen treatment. A significant, improvement in survival of 5.6% was seen in ER, node negative women as well. Tamoxifen therapy has bone protective effects, but has increased endometrial cancer and thromboembolic risks [42]

<table>
<thead>
<tr>
<th>Class</th>
<th>Agents in class</th>
<th>Mode of action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERM</td>
<td>Tamoxifen</td>
<td>Anti-oestrogenic effects in breast cancer</td>
<td>Before time menopause, hot flushes, retention of fluid, abnormal vaginal bleeding, uterine cancer risk, venous thromboembolism.</td>
</tr>
<tr>
<td>Aromatase Inhibitor</td>
<td>Anastrozole</td>
<td>Prevents production of the oestradiol</td>
<td>Hot flushes, joint pain, vaginal bleeding, increased risk of fracture due to decreased bone mineral density.</td>
</tr>
<tr>
<td></td>
<td>Letrozole</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exemestane</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LHRH analogue</td>
<td>Goserelin</td>
<td>Inhibits pituitary LH secretion causing the reduced oestradiol concentration</td>
<td>Hot flushes, joint pain, bone pain, decrease bone mineral density, obesity.</td>
</tr>
<tr>
<td>Progestin</td>
<td>Megestrol acetate</td>
<td>It has Anti-oestrogenic effects</td>
<td>May cause obesity, hot flushes.</td>
</tr>
<tr>
<td>Competitive anagonist</td>
<td>Fulvestrant</td>
<td>Might have Anti-oestrogenic effects</td>
<td>Pain at injection site, hot flushes.</td>
</tr>
</tbody>
</table>

SERM= selective oestrogenic receptor modulator; ER= oestrogen receptor; LHRH = luteinising hormone releasing hormone [42,43]

**Chemotherapeutic Options**

Chemotherapy abbreviated as chemo and sometimes CTX or CTx uses chemical substances (chemotherapeutic agents), especially one or more that are given as part of a standardized chemotherapy regimen to treat cancer. Chemotherapy may be given for curative purpose, or it may aim to prolong life or to decrease symptoms. Traditional chemotherapeutic agents are cytotoxic, they act by killing cells that proliferate rapidly. Chemotherapy also harms normal cells that divide rapidly under normal circumstances, i.e. cells in the bone marrow, digestive tract, and hair follicles. Due to this reason chemotherapy produce adverse side effects such as myelosuppression, mucositis, and alopecia (hair loss). Chemotherapy may be introduced as a one drug at a time (single-agent chemotherapy) or combination of several drugs at once (combination chemotherapy or polychemotherapy). Now days there are a number of strategies used in the administration of chemotherapeutic drug. Chemotherapy may be given with a curative purpose or it may aim to prolong life or to reduce symptoms. Combined modality chemotherapy is the use of drugs along with other cancer treatments, such as radiation therapy, surgery or hyperthermia therapy. Induction chemotherapy is used for curative purpose and is the first line of treatment of cancer with a chemotherapeutic drug. Consolidation chemotherapy is given after remission to prolong the overall disease-free time and improve the survival of patients. Combination chemotherapy involves the administration of a number of different drugs simultaneously to treat patients. The biggest advantage is decreasing the chances of resistance developing to any one agent Neoadjuvant chemotherapy is given prior to surgery, and is designed to shrink the primary tumor and also given to cancers with a high risk of micrometastatic disease. Adjuvant chemotherapy is given after radiotherapy or surgery and can be used when there is the risk of cancer recurrence. Maintenance chemotherapy is a repeated low-dose treatment to prolong relapse. Palliative chemotherapy is given without a curative purpose, but simply to decrease tumor load and increase life expectancy [44].

**Targeted therapy**

Breast cancer patients with positive HER2 protein, a monoclonal antibody, trastuzumab (Herceptin) is used to inhibit the activity of HER2 protein in cancer cells, slow down their growth. In advanced breast cancer cases, trastuzumab use in along with chemotherapy can both obstacle cancer growths as well as improve the prognosis. Several clinical trials reports confirmed that in adjuvant treatment, i.e. postoperative following breast cancer surgery, trastuzumab use for up to one year delays in the recurrence of breast cancer and improves patient survival [45]. Some other targeted therapies that fight cancer cells include Angiogenesis inhibitors. Angiogenesis inhibitors are antibodies prevent the growth of new blood vessels, disrupting the oxygen supply and nutrients to the cancer cells. Signal transduction inhibitor is another targeted therapy. These are antibodies inhibiting the cells division, stopping cancer from proliferating.
CR011-vcMMAE aka CDX-011 and Glematumumab vedotin is another an antibody-drug conjugate targeted at transmembrane glycoprotein NMB (GPNMB) that consists of human monoclonal antibody, CR011, linked to strong cell-killing drug, monomethyl-aursitatin E (MMAE). CR011-vcMMAE is currently in Phase II clinical trials evaluating its safety and effectiveness in the management of metastatic breast cancer, and in a Phase I trial to evaluate the safety and activity of alternate dosing schedules. [46]

Bevacizumab is another commercially available monoclonal antibody. This blocks the activation of the VEGF receptor. Bevacizumab delays disease progression over a period of five months over conventional chemotherapy, but survival outcome was not better. [46]

**Preclinical cancer preventive drug**

In March 2007, edition of scientific journal, Nature Genetics, from Canada's McGill University administered that they had make an effective drug target for treating breast cancers by hindering an enzyme called protein tyrosine phosphatase 1B (PTP1B), which has been used in inducing breast cancer in experimental mouse models [48].

Cholesterol drug - Ro 48-8071 stops cholesterol production and effective in destroying cancer cells as PRIMA-1, without affecting other normal breast cells. [49]

The combination of metformin and doxorubicin killed human cancer stem cells and non-stem cancer cells in culture. In a study, researchers used four genetically distinct breast cancer cell lines. In mice, pretreatment with a diabetes drug prevented the capability of breast cancer stem cells to form tumors. The dual therapy also regressed tumor mass rapidly and prevented recurrence for longer than doxorubicin alone. By alone, metformin was ineffective in treating cancers [49].

The preliminary research into flax seeds on rats indicates that flax can significantly alter breast cancer growth and metastasis, and enhances inhibitory effect of tamoxifen on estrogen-dependent tumors [50].

Stimuvax is an under evaluation cancer vaccine known to stimulate the body's immune system to identify and destroy cancer cells expressing MUC1, a glycoprotein antigen widely expressed on the common cancers [51].

**Medicinal plants in the treatment of breast cancer**

Screening of medicinal plant extracts for screening anticancer activity started in 1961 by National cancer institute of USA. In up to 1981 (about 20 years) 1,14,045 plants had been screened for anticancer activity of which only 3.4% have been observed to be active in one or more biological systems. Jiang et al has reported that Ganoderma lucidum retarded the growth of breast cancer cells by inhibiting the Akt/NF-kappaB signaling. It is used to treat cancer cells. It inhibits the transcription factor NF-kappaB and inhibits the invasive behavior of breast cancer cells. The exact mechanism for inhibition of cancer cells is not understood. Study showed that proliferation of breast cancer MDA-MB-231 cells is inhibited and Akt/NF-kappaB signaling is suppressed. Phosphorylation of Akt at Ser473 is suppressed by this plant and expression of Akt is suppressed, as a result NF-kappaB activity in MDA-MB-231 cells is inhibited [52].

Ray et al reported that Momordica charantia extract inhibits breast cancer by modulating cell cycle regulatory genes. This study was conducted in vitro models. Extract of this plant was investigated in breast cancer cells, MCF-7 and MDA-MB-231, and primary human mammary epithelial cells. This extract was able to decrease cell division and apoptotic cell death was induced. Surviving and claspin expression was inhibited by this extract [53].

Loo et al reported the efficacy of this plant in breast cancer. MDA-MB-231 breast cancer cell and normal human mammary gland cell were treated with a compound that contains Cathouse tinctorius. Inhibition of cell proliferation was observed by this compound. Inhibition of cell proliferation was dose dependent. This cytotoxic activity was more than commonly used cytotoxic drugs [54].
Gunver et al. reported the efficacy of *Viscum album* plant in breast cancer [55].

Pommier et al. reported the efficacy of *Calendula officinalis* for the prevention of acute dermatitis during irradiation for breast cancer [56].

*Citrullus colocynthis* plant has growth inhibitory activity. Cucurbitacin glucosides have been isolated from this plant. These glycosides prevent human breast cancer cells [57].

**CONCLUSION**

Epidemiology, diagnostic techniques and treatment of breast cancer has been reviewed. The literature review indicates that early diagnosis, treatment, awareness about the risk factors of breast cancer and education regarding self examination of breast cancer can decrease the death rate of breast cancer patient.

**Ethics Statement**

This is a review article and there is no need of approval from ethical committee

**Conflict of Interest:**

There is no conflict of interest

**Disclosure Statement**

None of the authors have a financial or proprietary interest in subject matter or materials discussed in manuscript, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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