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 clinicopathological 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

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

Table 2: Breast cancer survivors

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

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]. Sreedharan 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 thhe 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 te 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 doubhtful. 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)

Tx Primary tumor cannot be evaluated

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

a. Extension to chest wall not including pectoral muscle

b. Oedema, including peau d'orange, ulceration of skin or satellite skin nodules confined to he same breast

c. Both a and b

d. d. Inflammatory carcinoma.

Regional lymph nodes (N)

Nx Regional lymph node cannot be evaluated.

N0 No regional lymph node metastasis

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.

pN0 No regional lymph node metastasis.

pN1 a. Metastasis to 1 to 3 axillary lymph nodes

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.

pN3

a. Metastasis to 10 or more axillary lymph nodes (at least 1 tumour deposit more than   2 mm) or to infraclavicular lymph node

b. Metastasis to clinically-apparent ipsilateral internal mammary lymph node in the   presence of 1 or more positive axillary lymph nodes or to more than 3 axillary lymph nodes and to internal mammary lymph node with microscopic disease detected by sentinel lymph node dissection but not clinically-apparent.

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 radition therapy (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 3: Hormonal therapies for breast cancer treatment

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

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 mylosuppersion, 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.

Table 4: Commonly available chemotherapeutic agents and regimens in breast cancer patients [42,43]

Drug class	Agents in class	Mode of action	Specific adverse reaction
Anthracyclines	Doxorubicin (A); Epirubicin (E)	(anti-DNA action)	Irreversible cardiomyopathy, alopecia, myelosuppression, nausea, and vomiting.
Taxanes	Docetaxel (D); Paclitaxel	(interfere with DNA synthesis	Cardiotoxicity, Hepatic insufficiency. Sensory and motor neuropathy and fluid retention. Mild to moderate myalgias and arthralgias.
Alkalyting agents	Cyclophosphamide(C)	Inhibit DNA synthesis	May be associated with hemorrhagic cystitis
Pyrimidine analogues	5-Fluorouracil (F); Capecitabine	Inhibit DNA synthesis	Commonly cause GI disturbance
Folic acid analogues	Methotrexate (M)	Inhibit DNA synthesis	Ulcerative stomatitis

Table 5: Some therapeutic antibodies for breast cancer [47]

Monoclonal antibody	Target	Mode of action
Trastuzumab (Herceptin)	HER2 receptors protein	Block the ability of the cancer cells to receive chemical signals for cell growth
	HER2 receptors protein	Block the cancer cells' ability to receive growth signals.
Bevacizumzb (Avastin)	VEGF receptor protein in forming tumor blood vessels)	Block the growth of new blood vessels that cancer cells depend on to grow and function
Everolimus	mTOR	Works against hormone-receptor-positive breast cancers
Lapatinib	HER2 receptors proteins	Block certain proteins that can cause uncontrolled cell growth.

CR011-vcMMAE aka CDX-011 and Glembatumumab 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-auristatin 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 regress 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 tinctorious. 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.

REFERENCES

1. Majeed W, Bilal Aslam, Ijaz Javed, Tanweer Khaliq, et al (2014). Breast Cancer: Major Risk Factors and Recent Developments in Treatment *Asian Pac J Cancer Prev*, 15, 3353-3358.
2. Natalia B, Sonja H, Thilo D (2013). Hereditary breast cancer: ever more pieces to the polygenic puzzle. *Hered Cancer Clin Pract*, 11, 12.
3. Beiki O, Per Hall, Anders Ekbom and Tahereh Moradi (2012). Breast cancer incidence and case fatality among 4.7 million women in relation to social and ethnic background: a population-based cohort study. *Breast Cancer Res*, 14: 1-13.
4. Shamsi U, Khan S, Usman S, Soomro S, Azam I (2013). A Multicenter Matched Case Control Study of Breast Cancer Risk Factors among Women in Karachi, Pakistan. *Asian Pac J Cancer Prev*, 14, 183-8
5. Han SJ, Guo QQ, Wang T, et al (2013). Prognostic significance of interactions between ER alpha and ER beta and lymph node status in breast cancer cases. *Asian Pac J Cancer Prev*, 14, 6081-4.
6. Agnieszka M, Magdalena K, Grazyna J, Iwanowicz P (2014). Assessment of midwifery student preparation for reforming the role of breast cancer educator. *Asian Pac J Cancer Prev*, 15, 5633-5638
7. Haghighat S, Akbari M, Ghaffari S, Yavari P (2012). Standardized breast cancer mortality rate compared to the general female population of Iran. *Asian Pac J Cancer Prev*, 13, 5525-28.
8. Shaukat U, Ismail M, Mehmood N (2013). Epidemiology, major risk factors and genetic predisposition for breast cancer in the Pakistani population. *Asian Pac J Cancer Prev*, 14, 5625-9.
9. Kadivar M, Mafi N, Joulaee A, et al (2012). Breast cancer molecular subtypes and associations with clinicopathological characteristics in Iranian women, 2002-2011. *Asian Pac J Cancer Prev*, 13, 1881-6.
10. Memon ZA, Shaikh AN, Rizwan S, Sardar MB (2013). Reasons for patient's delay in diagnosis of breast carcinoma in Pakistan. *Asian Pac J Cancer Prev*, 14, 7409-14.
11. Harirchi I, Karbakhsh M, Kashefi A, Momtahen A (2004). Breast cancer in Iran: results of a multi-center study. *Asian Pac J Cancer Prev*, 5, 24-7
12. Khoker S, Muhammad UQ, Masooma R, Naseem A, Afaf S (2012). Clinicopathologic profile of breast cancer patients in Pakistan: ten years data of a local cancer hospital. *Asian Pac J Cancer Prev*, 13, 693-8.
13. Badar F, Faruqui ZS, Uddin N, et al (2011). Management of breast lesions by breast physicians in a heavily populated south Asian developing country. *Asian Pac J Cancer Prev*, 12, 827-32.
14. Melissa Marie Alegre, McKay Hovis Knowles, Richard A Robison, Kim Leslie O'Neill* Mechanics behind Breast Cancer Prevention - Focus on Obesity, Exercise and Dietary Fat Asian Pacific Journal of Cancer Prevention, Vol 14, 2013
15. Zainal NZ, Nik-Jaafar NR, Baharudin A, Sabki ZA, Ng CG (2013). Prevalence of depression in breast cancer survivors: a systematic review of observational studies. *Asian Pac J Cancer Prev*, 14, 2649-56.
16. Al-Naggar RA, Nagi NM, Ali MM, et al (2011). Quality of life among breast cancer patients in Yemen. *Asian Pac J Cancer Prev*, 12, 2335-41.
17. Jamal S, Mamoon N, Mushtaq S, et al (2006). Carcinoma of the male breast: a study of 141 cases from Northern Pakistan. *Asian Pac J Cancer Prev*, 7, 119-21.
18. Yang L, Parkin DM, Ferlay J, et al (2005). Estimates of cancer incidence in China for 2000 and projections for 2005. *Cancer Epidemiol Biomarkers Prev*, 14, 243-50.
19. Alco G, Igdem S, Dincer M, et al (2014). Vitamin D levels in patients with breast cancer: importance of dressing style. *Asian Pac J Cancer Prev*, 15, 1357-62
20. Abdull R, Noor N (2013). Cruciferous vegetables: dietary phytochemicals for cancer prevention. *Asian Pac J Cancer Prev*, 14, 1565-1570
21. Mary J, Vinotha P, Pradeep A (2012). Screening for *in vitro* cytotoxic activity of seaweed, Sargassum sp. against Hep-2 and MCF-7 cancer cell lines, *Asian Pac J Cancer Prev*, 13, 6073-6.
22. Zhu Y, Zhou L, Jiao S, Xu L (2011). Relationship between soy food intake and breast cancer in China, *Asian Pac J Cancer Prev*, 12, 2837-40
23. Dwivedi V, Shrivastava R, Hussain S (2011). Comparative anticancer potential of clove (*Syzygium aromaticum*)-an Indian spice--against cancer cell lines of various anatomical origin, *Asian Pac J Cancer Prev*, 12, 1989-93
24. Ferlay J, Soerjomataram I, Ervik M, et al (2012). Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11 [Internet].Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan. iarc.fr, accessed on 11/05/2014.

25. WHO (2006). Library Cataloguing in Publication Data Guidelines for management of breast cancer/by WHO Regional Office for the Eastern Mediterranean.

26. Redhwan A, Al-Naggar DH, Bobryshev YV, Chen R, Assabri A (2011). Practice and barriers toward breast self-examination among young Malaysian women. *Asian Pac J Cancer Prev*, 12, 1173-8.

27. Alipour S, Moini A, Jafari-Adli S, Gharaie N, Mansouri K (2012). Comparison of teaching about breast cancer via mobile or traditional learning methods in gynecology residents. *Asian Pac J Cancer Prev*, 13, 4593-5.

28. Sreedharan J, Muttappallymyalil J, Venkatramana M, Thomas M (2010). Breast self-examination and practice among nurses in United Arab Emirates. *Asian Pac J Cancer Prev*, 11, 651-4

29. Ozkan A, Malak AT, Gürkan A, San Turgay A (2010). Do Turkish nursing and midwifery students teach breast selfexamination to their relatives? *Asian Pac J Cancer Prev*, 11, 1569-73.

30. Ahmed B (2010). Awareness and practice of breast cancer and breast self examination among university students in Yemen. *Asian Pac J Cancer Prev*, 11, 101-6

31. Porika M, Malotu N, Veldandi U-K, et al (2010). Evaluation of tumor markers in Southern Indian breast cancer patients. *Asian Pac J Cancer Prev*, 11, 157-9.

32. Abdulkareem ST (2014). Breast magnetic resonance imaging indications in current practice. *Asian Pac J Cancer Prev*, 2, 569-75

33. Tarhan M-O, Gonel A, Kucukzeybek Y, et al (2013). Prognostic significance of circulating tumor cells and serum ca15-3 levels in metastatic breast cancer, single center experience, preliminary results. *Asian Pac J Cancer Prev*, 14, 1725-9.

34. Kanaga KC, Nithiya J, Shatirah MF (2011). Awareness of breast cancer and screening procedures among Malaysian women. *Asian Pac J Cancer Prev*, 12, 1965-7.

35. Aebi S T. Davidson, G. Gruber & F. Cardoso (2011). On behalf of the ESMO Guidelines Working Group Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 22, 12–24.

36. Polgár, C. Major, T. (2009). "Current status and perspectives of brachytherapy for breast cancer". *Int J Clin Oncol*, 14, 7–10.

37. Bennett, Joseph J. (2006). "Sentinel Lymph Node Biopsy for Breast Cancer and Melanoma". *US Oncol Dis*, 1, 16–19.

38. Nelson JC, Beitsch PD, Vicini, FA, et al (2009). "Four-year clinical update from the American Society of Breast Surgeons MammoSite brachytherapy trial". *The Amer J Surg*, 198, 83-91.

39. Nixon A, Manola J, Gelman R, et al (1998). No long-term increase in cardiac-related mortality after breast-conserving surgery and radiation therapy using modern techniques. *J Clin Oncol*, 16, 1374-1379.

40. Shapiro C, Hardenbergh P, Gelman R et al, (1998). Cardiac effects of adjuvant doxorubicin and radiation therapy in breast cancer patients. *J Clin Oncol*, 16, 3493-3501.

41. Early Breast Cancer Trialists' Collaborative Group (2000). Favourable and unfavorable effects on long-term survival of radiotherapy for early breast cancer: An overview of the randomized trials. *Lancet*, 355, 1757–1770.

42. Chris EH, Hyman BM (2003). Diagnosis and Treatment of Breast Cancer in the Elderly CA. *Cancer J Clin*, 53, 227–244.

43. National Medicines Information Centre ST. JAMES'S HOSPITAL • DUBLIN 8 2012; 18(1)

44. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al (2006). "Adjuvant Docetaxel or Vinorelbine with or without Trastuzumab for Breast Cancer". *New Eng J Med*, 354, 809–820.

45. Piccart-Gebhart, MJ, Procter M, Leyland-Jones B et al (2005). "Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer". *New Eng J Med* 353, 1659-1672

46. Hamid O, Sznol M, Pavlick AC, et al (2010). "Frequent dosing and GPNMB expression with CDX-011 (CR011-vcMMAE), an antibody-drug conjugate (ADC), in patients with advanced melanoma". *J Clin Oncol (Meeting Abstracts)* 28(15 Suppl): 8525.

47. Han-Chung Wu1, De-Kuan Chang, and Chia-Ting Huang, (2006). Targeted Therapy for Cancer. *J Cancer Mol*, 2, 57-66.

48. BBC News 2007

49. Medical News today 2011 www.medicalnewstoday.com

50. Wang L. Chen J, Thompson LU. (2005). "The inhibitory effect of flaxseed on the growth and metastasis of estrogen receptor negative human breast cancer xenografts is attributed to both its lignan and oil components". *Int J Cancer*, 116,793-798

51. Medical News today 2009. www.medicalnewstoday.com/

52. Jiang J, Slivova V, Harvey K (2004). *Ganoderma lucidum* suppresses growth of breast cancer cells through the inhibition of Akt/NF-kappaB signaling. *Nutr Cancer* 49:209-216.

53. Ray B, Raychoudhuri A, Steele R (2010). Bitter melon (*Momordica charantia*) extract inhibits breast cancer cell proliferation by modulating cell cycle regulatory genes and promotes apoptosis. *Cancer Res*, 70, 1925-1931.

54. Loo T, Cheung N, Chow W (2004). The inhibitory effect of herbal formula comprising ginseng and *Carthamus tinctorius* on breast cancer. *Life Sci*, 76:191-200.

56. Gunver S, Anja G, Michael S (2009). *Viscom album* extracts in breast and gynaecological cancers: a systematic review of clinical and preclinical research. *J Exp Clin Cancer Res*, 28, 79-83.

57. Pommier P, Gomez F, Sunyach MP, D'Hombres A, Carrie C, Montbarbon X (2004). Phase III randomized trial of Calendula officinalis compared with trolamine for the prevention of acute dermatitis during irradiation for breast cancer. J. Clin. Oncol. 22: 1447–1453

58. Tannin T, Grossman S, Dovrat S (2007). Growth inhibitory activity of cucurbitacin glucosides isolated from *Citrullus colocynthis* on human breast cancer cells. *Biochem Pharmacol*, 73, 56-67.