The Pharma Innovation Journal 2019; 8(5): 57-62

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2019; 8(5): 57-62

www.thepharmajournal.com
Received: 01-03-2019
Accepted: 05-04-2019

A Ananya
Department of Pharmacy Practice, Care College of Pharmacy, Warangal, Telangana, India

D Sudheer Kumar
Department of Pharmaceutics, Care College of Pharmacy, Warangal, Telangana, India

P Kishore
Department of Pharmacy Practice, Care College of Pharmacy, Warangal, Telangana, India

Correspondence
P Kishore
Department of Pharmacy Practice, Care College of Pharmacy, Warangal, Telangana, India

A review on breast cancer

A Ananya, D Sudheer Kumar and P Kishore

Abstract
Cancer is a malignant growth resulting from uncontrolled division of abnormal cells. Breast cancer is the second leading cause of cancer death among women. The cause of breast cancer is not known although multiple factors like genetics, life style and hormonal imbalances predispose breast cancer. It usually presents with lump in either side of the breast with or without other symptoms like breast changes, pain and nipple discharge. Radiological examination is the mainstay for breast cancer screening and detection. Early diagnosis ameliorates survival rate. Treatment modalities available for breast cancer are surgery, chemotherapy, radiotherapy, immunotherapy, targeted therapy and complementary alternative medicine. The main objectives of treatment are to reduce local tumor recurrence, risk of metastasis and to improve patient quality of life with minimal adverse effects. Diet and life style plays a key role in prognosis and quality of life of cancer treated patients.

Keywords: Breast cancer, mastectomy, chemotherapy, breast feeding

Introduction
Definition: Breast cancer is the tumor that develops from breast tissue characterized by unrestricted abnormal cell proliferation in the milk production glands (lobules) and or passages (ducts) of the breast [1]. In Majority of the cases tumor initiates in the ducts of the breast (ductal cancers). Breast cancer is the most common invasive cancer in women worldwide.

Epidemiology
Globally, over one million women are diagnosed with breast cancer every year. Every year more than 500,000 women die from this disease [2]. In 2017-2018 about 252,710 new cases of invasive breast cancer, 63,960 new cases of non-invasive breast cancer were diagnosed in women and 2,470 cases were diagnosed in men [1]. Based on Surveillance, Epidemiology, and End Results (SEER) database, the probability of a woman developing breast cancer is a lifetime risk of 1 in 8, 1 in 202 from birth to age 39 years of age, 1 in 26 from 40-59 years, and 1 in 28 from 60-69 years [3]. Breast cancer has second highest cancer mortality rate of 27.2 per 100,000 [4].

Risk factors (3)
1. Genetic factors
About 20%-25% of women with breast cancer have a positive family history. High-risk predisposition alleles include mutations in BRCA1, BRCA3, TP53 gene, PTEN, STK11, Neurofibromatosis (NF1) and (CDH-1) E-Cadherin accounts a 40 %-85 % lifetime risk of developing breast cancer. Moderate risk genes including homozygous ataxia-telangiectasia (ATM) mutations, somatic mutations in tumor suppressor gene CHEK2, and BRCA1 and BRCA2 modifier genes BRIP1 and PALB2 accounts a 20 %-40 % lifetime risk of breast cancer. Development of breast cancer clustered in Families results from the interaction between lifestyle factors and these genetic risk variations.

2. Reproductive factors
Early menarche: Early menarche (below age 12) is a risk factor of breast cancer in both pre and post-menopausal women. Delay in menarche have a protective effect on breast cancer. Delay by two years is associated with corresponding risk reduction of 10 %.

Parity and age at first pregnancy: Nulliparous women have high risk of developing breast cancer compared to parous women. Younger age at first pregnancy and greater number of children before age 35 have a protective effect against breast cancer. Advanced age at first full

term pregnancy can raise a risk of developing breast cancer than that of a nulliparous woman.

Breast feeding: Breast feeding has a defensive out- turn against breast cancer. Breast feeding typically delays the onset of ovulation and drop in normal sex harmone levels. It has been estimated that there is a 4.3% reduction for every one-year of breast feeding.

Menopausal age: Later onset of menopause is associated with increased risk of breast cancer. Every year delay in the onset of menopause confers a 3% increase in risk and every five-year delay in the onset of menopause confers a 17% increase in risk of breast cancer.

3. Hormonal factors

Breast cancer risk is high in HRT users (>5 years) compared to non-HRT users. Data from the Nurses' Health Study, suggest that women who are on unopposed postmenopausal estrogen increase their risk of breast cancer by 23 % at age 70. High endogenous sex hormone levels (predominantly testosterone) increase the risk of breast cancer in both premenopausal and postmenopausal women.

4. Life style factors

Alcohol consumption: Intake of alcohol about 5.0 to 9.9 g per day has been associated with increased risk of breast cancer.

Physical activity: Consistent physical activity has been shown a conservative effect on breast cancer. Physical inactivity together with other risk factors account for 21% of all breast cancer deaths worldwide.

Obesity: Obesity augments risk of breast cancer specifically in post-menopausal women. Postmenopausal breast cancer risk is about 1.5 times higher in overweight women and about 2 times higher in obese women than in lean women [5]. Insulin resistance and hyperinsulinemia supplements the probability of developing cancer. Insulin has anabolic effects on cellular metabolism and insulin receptor overexpression has been demonstrated in human cancer cells.

Diet: There is a strong relationship between diet and breast cancer. Studies connote that soy intake is inversely associated with breast cancer risk in Asian but not Western populations [6]. Intake of Carotenoids, micronutrients in fruits and vegetables reduce the risk of HR breast cancers [7].

Smoking: Tobacco smoking is linked to greater risk of breast cancer. American Cancer Society found that women who initiated smoking before the birth of their first child had a 21 % higher risk of breast cancer than women who never smoked [8].

Radiation: Radiation exposure from various sources including treatment of childhood cancer and nuclear explosion increases the risk of breast cancer.

Clinical features

Symptoms in women [9].

- Lump in the breast
- Tendery lump area
- Breast pain
- Nipple discharge
- Nipple retraction
- Nipple eczema
- Swelling of breast
- A lump in the underarm area
- Skin irritation or dimpling around breast
- Ulceration over lump
- Skin fixation over lump

Symptoms in Men

- Lump in the breast
- Nipple inversion

Pathophysiology [10, 11].

Tumor in the breast usually begins as ductal hyper proliferation and then develops into benign tumor or even metastatic carcinoma after constant stimulation by various carcinogenic factors. Tumor microenvironments such as the stromal influences or macrophages play vital roles in breast cancer initiation and progression. Only stromal exposure to carcinogens can hit the tumor genesis. Macrophages generate a mutagenic inflammatory microenvironment, which can promote angiogenesis and enable cancer cells to escape from immune rejection.

There are two theories to explain genesis and progression of breast cancer- cancer stem cell theory and stochastic theory. Cancer stem cell theory suggests that all tumor subtypes are derived from the same stem cells or progenitor cells. Acquired genetic and epigenetic mutations in the progenitor cells lead to different tumor phenotypes. The stochastic theory suggests that each tumor subtype is initiated from a single cell type. Random mutations can gradually accumulate in any breast cells, leading to their transformation into tumor cells or neoplasm.

Lot of genes have been associated in breast cancer expression. Mutations and abnormal amplification of genes (oncogenes, anti-oncogenes) play key role in the processes of tumor initiation and progression. High-penetrance genes (BRCA1, BRCA2, p53, PTEN, ATM, NBS1, or LKB1), low-penetrance genes such as cytochrome P450 genes (CYP1A1, CYP2D6, CYP19), glutathione S-transferase family (GSTM1, GSTP1), alcohol and one-carbon metabolism genes (ADH1C and MTHFR), DNA repair genes (XRCC1, XRCC3, ERCC4/XPF), and genes encoding cell signaling molecules (PR, estrogen receptor (ER), TNF-alpha, or heat shock protein 70 (HSP70)) are factors contributing in the pathophysiology of breast cancer. Breast cancer associated gene 1 and 2 (BRCA1 and BRCA2) are two famous anti-oncogenes for breast cancer. Mutations in either BRCA1 or BRCA2 genes may trigger the tumor formation by dysregulating the normal cell proliferation. The other important oncogene in breast cancer is Human epidermal growth factor receptor 2, also known as c-erbB-2. Gene amplification and re-arrangement of HER2 gene may result in breast cancer risk. Oncogene EGFR, also known as c-erbB-1 or Her1 have a role in cell proliferation, cell invasion, angiogenesis and anti-apoptosis. Overexpression of EGFR is found in more than 30 % of cases of the inflammatory breast cancer. Other related genes are c-Myc, Ras gene family (H-Ras, K-Ras and N-Ras).

Staging [9].

TNM Staging System

TNM system is the most widely used cancer staging system.

- The T refers to the size and extent of the main tumor. The

main tumor is usually called the primary tumor.
- The N refers to the the number of nearby lymph nodes that have cancer.
- The M refers to whether the cancer has metastasized. This means that the cancer has spread from the primary tumor to other parts of the body.
- According to American Joint Commission on Cancer guidelines–tumor node metastasis classification

Primary tumor (T)
Based on the tumor size, they are categorized as TX, T0, Tis (DCIS), Tis (LCIS), Tis (Paget's), T1, T1mi, T1a, T1b, T1c, T3, T4, T4a, T4b, T4c and T4d
TX - Primary tumor cannot be assessed
T0 - No evidence of primary tumor
T3 - Tumor > 50 mm in greatest dimension

Regional lymph nodes (N)
Based on no. of lymph nodes and type of lymph nodes involved, they are categorized as NX, NO, N1, N2, N2a, N3, N3a, N3b, N3c
NX - Regional lymph nodes cannot be assessed (for example, previously removed)
N0 - No regional lymph node metastases
N1 - Metastases to movable ipsilateral level I, II axillary lymph node(s)

Distant metastases (M)
M0 - No clinical or radiographic evidence of distant metastases
cM0(i +) - No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other non-regional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1 - Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

Grading [12].
Grading compares the appearance of the breast cancer cells to normal breast tissue. Usually Cancer cells are poorly differentiated or undifferentiated. Cancer cells are classified into well differentiated (low grade), moderately differentiated (intermediate grade), and poorly differentiated (high grade).

Diagnosis
Diagnosis includes the triad of clinical, radiological and pathological examinations. Clinical examination includes bimanual palpation of the breasts and local regional lymph nodes. Radiological examination includes mammography, ultrasound and Magnetic resonance imaging of the breasts and regional lymph nodes. Pathological examination includes fine needle aspiration and biopsy [13].

Breast self and clinical breast examination: The 2013 NCCN guidelines recommend annual clinical breast examination (CBE) for women of average risk 20-39 or > 40 years of age as well as BSE to develop and exhibit breast self-awareness. Physical examination includes a careful visual inspection for specific symptoms like Nipple changes, asymmetry, obvious masses, breast pain, breast discharge and breast changes such as dimpling, erythema, discoloration [13].

Molecular breast imaging (MBI): In this test, a slightly radioactive drug called a tracer is injected into a vein. The tracer attaches to breast cancer cells and is detected by a special camera. This technique is also called Miraluma test, sestamibi test, scintimammography, or specific gamma imaging.

FISH test: This test used to identify the presence of specific chromosomes or chromosomal regions through hybridization (attachment) of fluorescently labeled DNA probes to denatured chromosomal DNA [14].

Blood-based assay (Serum tumor biomarkers): Breast biomarkers (CA 15-3, Carcinoembryonic antigen (CEA), and CA 27-29) use is restricted only in metastatic breast cancers [11].

Gene assays: Oncotype DX is a reverse transcription polymerase chain reaction-based assay used to determine the prognosis of patients with breast cancer and can be used for all tumors, including node-positive, HER- 2 neu-positive, and ER/PR-negative disease [3].

Treatment
Surgery, chemotherapy, radiation therapy, immunotherapy, targeted therapy and complementary alternative medicine are available treatment options for breast cancer. The choice of treatment depends on tumor biology, lymph node extensions, demographics, patient health status, body habitus and patient's preferences [14]. Preserving fertility and preventing premature ovarian failure (POF) is one of the most important considerations in young breast cancer patients.

Surgery
Types of mastectomy includes
1. TM or simple mastectomy: removal of the breast
2. MRM or modified radical mastectomy: TM+ axillary lymph node dissection.
3. RM or radical mastectomy which includes removal of the pectoralis muscles and level III axillary nodes.
4. Prophylactic mastectomy (PM): removal of breast when there is no cancerous tumor in the breast.

In total mastectomy arm, axillary dissection was performed only if lymph nodes were positive.

Lumpectomy with surgical axillary staging
Negative axillary nodes (Tumor free lymph nodes): Radiation therapy to whole breast with or without boost (by photons, brachytherapy, or electron beam) to tumor bed followed by chemotherapy.

One-three positive axillary nodes: Radiation therapy to whole breast with or without boost (by photons, brachytherapy, or electron beam) to tumor bed and radiation therapy to infraclavicular, supraclavicular and internal mammary nodes.

Four positive axillary nodes: Radiation therapy to whole breast with or without boost (by photons, brachytherapy, or electron beam) to tumor bed, infraclavicular region and supraclavicular area followed by chemotherapy.
Total mastectomy with surgical axillary staging with or without reconstruction

Negative axillary nodes (Tumor free lymph nodes) and tumor ≤ 5 cm and margins ≥ 1 mm: No radiation therapy needed, advise post chemotherapy radiation therapy to chest wall and internal mammary nodes.

One-three positive axillary nodes: post chemotherapy radiation therapy to chest wall, infra clavicular and supraclavicular areas.

Four positive axillary nodes: Post chemotherapy radiation therapy to chest wall, infra clavicular, supraclavicular areas and internal mammary nodes [3].

Radiation therapy

Radiation therapy is an adjuvant treatment for most women underwent surgery. Recurrence can be prevented by radiation. Radiation therapy uses high-energy X-rays or gamma rays that target a tumor or tumor site to kill the cancerous cells but it may also affect the other fast-growing cells. Types of radiation therapy includes whole breast radiation therapy (WBRT), accelerated partial breast irradiation (APBI), post mastectomy radiation therapy (PMRT) and Regional irradiation.

Dose Fractionation [15].

- Standard whole breast dose is 42.5 Gray (Gy) in 16 daily fractions.
- Certain patients are at risk for inferior cosmetic outcome from the 16-fraction course. Extended fractionation should be considered for patients with very large breast size, and those with significant post-operative induration, edema, erythema, hematoma or infection. Patients with these indications for extended fractionation should receive 45Gy in 25 daily fractions plus a boost dose of 10Gy in 5 fractions or 50.4 Gy in 28 daily fractions.
- If a boost is used, an additional dose of 6-16 Gy in 3-8 fractions is recommended.

Chemotherapy

Initiate chemotherapy within 12weeks of surgical removal of the primary tumor. Optimal duration of adjuvant treatment is unknown but appears to be 12 to 24weeks, depending on the regimen used.

Adjuvant Chemotherapy Regimens for Breast Cancer (16)

AC: Doxorubicin 60 mg/m^2 IV, day 1and Cyclophosphamide 600 mg/m^2 IV, day. Repeat cycles every 21 days for 4 cycles

FAC: Fluorouracil 500 mg/m^2 IV, days 1 and 4, Doxorubicin 50 mg/m^2 IV continuous infusion over 72 hours and Cyclophosphamide 500 mg/m^2 IV, day 1. Repeat cycles every 21–28 days for 6 cycles

TAC: Docetaxel 75 mg/m^2 IV, day 1, Doxorubicin 50 mg/m^2 IV bolus, day 1 and Cyclophosphamide 500 mg/m^2 IV, day 1 (doxorubicin should be given first). Repeat cycles every 21 days for 6 cycles (must be given with growth factor support)

Paclitaxel → FAC: Paclitaxel 80 mg/m^2 per week IV over 1 hour every week for 12 weeks Followed by Fluorouracil 500 mg/m^2 IV, days 1 and 4, Doxorubicin 50 mg/m^2 IV continuous infusion over 72 hours and Cyclophosphamide 500 mg/m^2 IV, day 1. Repeat cycles every 21–28 days for 4 cycles.

CEF: Cyclophosphamide 75 mg/m^2 per day orally on days 1–14, Epirubicin 60 mg/m^2 IV, days 1 and 8 and Fluorouracil 600 mg/m^2 IV, days 1 and 8. Repeat cycles every 21 days for 6 cycles (requires prophylactic antibiotics or growth factor support)

Recurrence rates are probably due to presence of micro metastatic disease in 10 %-30 % of LN-negative and in 35 %-90 % of LN-positive patients at the time of diagnosis. Adjuvant chemotherapy eliminates residual local or distant residual microscopic metastatic disease.

For Locally advanced or in borderline breast cancer where tumor-to-breast size ratio cannot be excised, neo adjuvant chemotherapy (4 cycles of doxorubicin plus cyclophosphamide) is advised. Women receiving neo-adjuvant therapy had a higher rate of pathologic negative axillary lymph nodes at surgery and increases the eligibility of breast conservative surgery.

HER2-positive disease

1. Adjuvant endocrine therapy / Adjuvant chemotherapy with trastuzumab
2. Adjuvant endocrine therapy + Adjuvant chemotherapy with trastuzumab
3. Adjuvant endocrine therapy + Adjuvant chemotherapy with trastuzumab + lymphnode dissection if LN's positive.

HER2-negative disease

Consider Adjuvant endocrine therapy or adjuvant chemotherapy with trastuzumab followed by endocrine therapy or combination of endocrine and chemotherapy with node dissection.

Triple negative disease

Consider adjuvant chemotherapy [12].

Estrogen positive breast cancer

Consider hormonal therapy or combination of endocrine and chemotherapy.

Targeted therapy

Targeted therapy is a current approach to tackle breast cancer in combination with or without chemotherapy. They often target specific biological processes responsible for tumor initiation and progression. Targeted therapy acts by many possible mechanisms – inhibiting proteins like mTOR, HER2 and enzyme Poly ADP ribose polymerase (PARP), blocking angiogenesis and interrupting CDK signaling. In advanced cases, trastuzumab can be used in combination with chemotherapy to delay cancer growth and improve the patient's survival [12].

Table 1: List of agents used in the treatment of breast cancer [12, 16].

Drug	Dosage regimen	Side effects
Aromatase Inhibitors: Nonsteroidal Anastrozole Letrozole	1 mg orally daily 2.5 mg orally daily	Bone loss/osteoporosis, hot flashes, myalgia/arthralgia, vaginal dryness/atrophy, mild headaches and diarrhea
Aromatase Inhibitor: Steroidal Exemestane	25 mg orally daily	Same as Nonsteroidal aromatase inhibitors

Antiestrogens: SERMs Tamoxifen Toremifene	20 mg orally daily 60 mg orally daily	Tumor flare and hypercalcemia
Antiestrogen: SERD Fulvestrant	250–500 mg or 500 mg IM every 28 days (after loading days 1, 15, 29)	Hot flashes, vaginal bleeding, mood changes, dizziness, headache, trouble sleeping, trouble breathing.
LHRH Agonists Goserelin Leuprolide Triptorelin	3.6 mg SC every 28 days 3.75 mg IM (SC) every 28 days 3.75 mg IM every 28 days	Nausea, liver problems, and tiredness, worsening of hot flashes, loss of sexual interest, bone thinning, vaginal dryness
Progestins Megestrol acetate Medroxyprogesterone	40 mg- 80mg orally 4 times a day 400–1000 mg IM every week	Weight gain, fluid retention, and thromboembolic events.
Androgens Fluoxymesterone	10 mg- 20mg orally twice a day	Headache, skin color changes, increased/decreased sexual interest, oily skin, hair loss and acne.
Estrogens Ethinyl estradiol Conjugated estrogens	1 mg orally 3 times a day 2.5 mg orally 3 times a day	Hot flashes, Vaginal discharge, Vaginal dryness or irritation, Fatigue, Nausea, Joint and muscle pain, Impotence in men with breast cancer.
Trastuzumab	Loading dose: 8mg/kg, followed by 6mg/kg q3week	Hot flashes, anemia, neutropenia, insomnia, fatigue, dyspnea.
Lapatinib	1250 mg PO every Day on Days 1-21 continuously	Increased LFT's, cardiovascular events, thrombocytopenia.
Neratinib	240 mg PO every Day with food continuously for 1 year	Decreased appetite, nail changes, weight loss, dry mouth.
Everolimus	10 mg PO every Day with or without food	Menstrual irregularities, hypertensive crisis, Arterial thrombotic events
Olaparib	300 mg po BD, continue until disease progression is subsided.	Anemia, abdominal cramps, urinary tract infection.
Pertuzumab	840 mg IV infusion over 60 min, then 420 mg IV infusion over 30-60 min q 3Weeks	Alopecia, peripheral neuropathy, mucositis, increased lacrimation, nail disorder.
Nivolumab	3 mg/kg	Skin peeling, cough, upper respiratory tract infection, swelling of the extremities, shortness of breath
Pembrolizumab	200 mg IV every 3 weeks	Fatigue, alopecia, nausea, neutropenia, and peripheral neuropathy.
Durvalumab	10 mg/kg IV q2wk	Musculoskeletal pain, constipation, decreased appetite, nausea, swelling of extremities, urinary tract infection
Ipilimumab	1mg/kg administered intravenously over a 90-minute period every 3 weeks for a total of 4 doses	Infusion-related reactions, Musculoskeletal pain, Constipation, Decreased appetite/hypophagia, Pyrexia/tumor associated fever, Abdominal pain, Diarrhea/colitis, Hyponatremia, grades 3-4, Lymphopenia.

Prevention of recurrence

1. **Anti-Estrogens:** Tamoxifen, Toremifen
2. **Aromatase inhibitors:** Anastrazole, Letrozole, Exemestane
3. **GnRH analogue:** Leuprolide

Patient counseling

Life style modifications

- According to Canadian Cancer Society and the American Cancer Society, patients should be engaged in at least 30 minutes of moderate-intensity physical activity at least five days of the week or 75 minutes of more vigorous exercise along with two to three weekly strength training sessions, including exercises for major muscle groups.
- Quit smoking and alcohol consumption. Smokers have an increased risk of venous thrombosis apart from breast cancer.
- Avoid drinking alcohol. High intake of alcohol (> 20 g/d) was associated with higher breast cancer mortality [17].
- Breast feeding has beneficial effects for both mother and infant. Breast feeding for 12 months decreases the risk of breast cancer in women.
- Avoid night shifts. High amounts of melatonin may increase the risk of breast cancer.
- Avoid stress. Perform yoga to maintain a healthy and peaceful life.

Diet

- Excess dietary intake of lipids and carbohydrates can influence metabolic- hormonal processes and may result in breast cancer metastasis and breast cancer mortality. Women with breast cancer should be encouraged to reduce their dietary fat intake by 15 %.
- Mediterranean diet (a diet rich in vegetables, unsaturated fats, fruits, fish and whole grains and limited intake of red meat and simple carbohydrates) had a beneficial effect on breast cancer survival.
- Soybeans contain both soy isoflavones (phytoestrogens) and soy proteins which have a positive impact on apoptosis, anti-angiogenesis and harmone regulation. Consume soya containing foods like edamame, tofu, tempeh and miso soup
- Vitamin D exhibits pro-differentiation and anti-proliferation properties. Low levels of vit D is associated with an increased risk of cancer related mortality. Intake of vitamin D foods lowers breast cancer recurrence. (17)
- Cut down processed foods and red meat. Consumption of well-over cooked red meat is associated with increased risk of BC.
- n-3 polyunsaturated fatty acids (n-3 PUFA) has been shown to decrease the risk of breast cancer by inhibiting carcinogenesis.

- Glycaemic control is advisable in breast cancer women with diabetes mellitus.
- Fruits and vegetables contain high content of polyphenols and fibres which have a protective impact on breast cancer.
- Women with breast cancer should be advised to take good amounts of strawberry, blueberry and lycopene containing fruits and vegetables such as red carrots, watermelons and papaya [18].

Conclusion

Although considerable advancement has been made in breast cancer prevention in the last decade, there is still lack of effective therapies that focuses on breast cancer prevention and recurrence. Early detection of breast cancer prevents cancer related mortality. Regular self-breast examination and checkup can reduce the incidence and cancer burden. Tumor size, grade and nodal status (Nottingham prognostic index) have a significant impact on disease sequelae. Effective collaboration amongst surgical oncologist, medical oncologists, radiation oncologists, nurses, geneticist, reconstructive surgeons and pharmacists are essential for better patient care and satisfactory treatment outcome. Clinical pharmacist should counsel the patients regarding life style changes, impact of diet in cancer and educate women on self-examination of breast for early detection of breast cancer through health awareness programs and seminars. Clinical pharmacist should implicate a positive attitude in cancer patients to improve their quality of life and achieve best treatment outcome.

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