

# Breast Cancer: Insights into Risk Factors, Pathogenesis, Diagnosis and Management

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Received August 30, 2015; Revised September 11, 2015; Accepted September 13, 2015

**Abstract** Breast cancer is the most common invasive cancer in females worldwide. It usually presents with a lump in the breast with or without other manifestations. Diagnosis of breast cancer depends on physical examination, mammographic findings and biopsy results. Treatment of breast cancer depends on the stage of the disease. Lines of treatment include mainly surgical removal of the tumor followed by radiotherapy or chemotherapy. Other lines including immunotherapy, thermochemotherapy and alternative medicine may represent a hope for breast cancer patients.

**Keywords:** breast, cancer, pathogenesis, diagnosis, management

**Cite This Article:** Ahmed M. Kabel, and Fahad H. Baali, "Breast Cancer: Insights into Risk Factors, Pathogenesis, Diagnosis and Management." *Journal of Cancer Research and Treatment*, vol. 3, no. 2 (2015): 28-33. doi: 10.12691/jcrt-3-2-3.

## 1. Introduction

Breast cancer is cancer that develops from breast tissue. It is the most common invasive cancer in women [1]. Signs of breast cancer include a lump in the breast, a change in breast shape, dimpling of the skin, nipple discharge or a red scaly patch of skin [2]. Risk factors for developing breast cancer include: female sex, obesity, lack of physical exercise, drinking alcohol, hormone replacement therapy during menopause, ionizing radiation, early age at first menstruation and old age [3]. Breast cancer most commonly develops in cells lining the milk ducts and the lobules that supply the ducts with milk. There are more than 18 subtypes of breast cancer [4]. Diagnosis of breast cancer is confirmed by taking a biopsy of the concerning lump. Once the diagnosis is made, further tests are done to determine if the cancer has spread beyond the breast and which treatments it may respond to [2].

Medical treatment of breast cancer with antiestrogens such as tamoxifen or raloxifene may prevent breast cancer in those who are at high risk of developing it [4]. Surgical removal of both breasts is another preventative measure in some high risk women. In those who have been diagnosed with cancer, various lines of treatment are used, including surgery, radiation therapy, chemotherapy, hormonal therapy and targeted therapy. In those with distant metastasis, treatments are mostly aimed at improving quality of life and survival rate [5].

## 2. Risk Factors for the Development of Breast Cancer

Risk factors for breast cancer include female sex, older age, genetics, lack of childbearing or lack of breastfeeding, higher levels of estrogens, certain dietary patterns, exposure to radiation, positive family history of breast cancer and obesity. Tobacco smoking appears to increase the risk of breast cancer. In those who are long-term smokers, the risk is increased 35% to 50% [6,7,8]. Oral contraceptives might represent a predisposing factor for the development of premenopausal breast cancer [9]. There is a relationship between diet and breast cancer, including an increased risk with a high fat diet, alcohol intake, obesity and high cholesterol intake [10,11]. Dietary iodine deficiency may also play a role [12].

Genetic susceptibility may play a significant role in the development of breast cancer by causing a hereditary breast-ovarian cancer syndrome. This includes those who carry the BRCA1 and BRCA2 gene mutation. Other significant mutations include p53 (Li-Fraumeni syndrome), PTEN (Cowden syndrome), and STK11 (Peutz-Jeghers syndrome) [13]. Moreover, certain diseases of the breast such as atypical ductal hyperplasia and lobular carcinoma in situ, are correlated with an increased breast cancer risk. Diabetes mellitus might also increase the risk of breast cancer [14].

Family history remains one of the most important risk factors for the development of breast cancer [15]. Women with a strong family history of breast cancer may inherit some genetic mutations that modify the risk factors of the disease and its clinicopathological features. The characteristics of familial breast cancer remain a controversial issue as several studies have shown inconsistent results [16]. Many studies have revealed that familial breast cancer has some specific clinical features compared to sporadic cases. It has been shown that

women diagnosed with positive family history usually present an early age of onset, bilateral breast cancer, advanced stage, lymph node involvement and negative hormone receptors with a less favorable prognosis [17].

### 3. Pathophysiology of Breast Cancer

Breast cancer usually occurs due to an interaction between environmental and genetic factors. PI3K/AKT pathway and RAS/MEK/ERK pathway protect normal cells from cell suicide. When the genes encoding these protective pathways are mutated, the cells become incapable of committing suicide when they are no longer needed which then leads to cancer development. These mutations were proven to be experimentally linked to estrogen exposure [18]. It was suggested that abnormalities in the growth factors signaling can facilitate malignant cell growth. Over expression of leptin in breast adipose tissue leads to increased cell proliferation and cancer [19].

The familial tendency to develop breast cancers is called hereditary breast-ovarian cancer syndrome. Some mutations associated with cancer, such as p53, BRCA1 and BRCA2, occur in mechanisms to correct errors in DNA leading to uncontrolled division, lack of attachment, and metastasis to distant organs. The inherited mutation in BRCA1 or BRCA2 genes can interfere with repair of DNA cross links and DNA double strand breaks [20]. GATA-3 directly controls the expression of estrogen receptor (ER) and other genes associated with epithelial differentiation. Loss of GATA-3 leads to inhibition of differentiation and poor prognosis due to increased cancer cell invasion and distant metastasis [21].

### 4. Clinical Presentation of Breast Cancer

The first presentation of breast cancer is typically a lump that is different from the rest of the breast tissue. Other presentations include thickening different from the other breast tissue, one breast becoming larger or lower, change in the position or shape of the nipples, skin dimpling, nipple discharge, constant pain in part of the breast or armpit or swelling beneath the armpit [22].

Inflammatory breast cancer is a particular type of breast cancer that usually presents with itching, pain, swelling, nipple inversion, warmth and redness throughout the breast, as well as an orange-peel texture to the skin referred to as peau d'orange. Paget's disease of the breast is another type of breast cancer that usually presents with redness, discoloration, or mild flaking of the nipple skin. Then, tingling, itching, increased sensitivity, burning pain and discharge from the nipple appear [23]. Phyllodes tumors are hard, movable non-cancerous lumps formed within the stroma of the breast and contain glandular as well as stromal tissue. They are classified on the basis of their appearance under the microscope as benign, borderline or malignant. Occasionally, breast cancer may present as metastatic disease. Common sites of metastasis include bone, liver, lung and brain. Symptoms depend on the site of metastasis and include unexplained weight loss, fever, chills, bone pains, jaundice or neurological symptoms [24].

### 5. Diagnosis of Breast Cancer

Physical examination of the breasts by a healthcare provider and mammography are considered as the primary tools for diagnosis of breast cancer [25]. Fine needle aspiration and cytology can also help to establish the diagnosis with a good degree of accuracy. Other types of biopsy include core biopsy or an excisional biopsy, in which the entire lump is removed. Imaging techniques such as ultrasound, computed tomography or magnetic resonance imaging are sufficient to give the physician accurate diagnosis and staging of the disease [26].

### 6. Classification of Breast Cancer

Breast cancers are often classified by several systems which can affect the prognosis and the response to treatment. Description of a breast cancer optimally includes all of these factors. They include histopathology, grade, stage, receptor status and DNA assays. Most breast cancers are derived from the epithelial lining of the ducts or lobules, and these cancers are classified as ductal or lobular carcinoma. Carcinoma in situ is growth of precancerous cells within a particular part of the breast without invasion of the surrounding tissue. Invasive carcinoma, however, penetrates into the surrounding tissues and may be associated with distant metastasis [27].

Grading often compares the appearance of the breast cancer cells to the appearance of normal breast tissue. Cancerous cells are usually poorly differentiated or undifferentiated. Cell division becomes uncontrolled and cell nuclei become less uniform. Pathologists describe cells as well differentiated (low grade), moderately differentiated (intermediate grade), and poorly differentiated (high grade) as the cells progressively lose the features seen in normal breast cells. Poorly differentiated cancers have the worst prognosis [23].

Breast cancer staging using the TNM system is based on the size of the tumor (T), whether or not the tumor has spread to the lymph nodes (N), and whether the tumor has metastasized (M). Stage 0 is a pre-cancerous, either ductal carcinoma in situ or lobular carcinoma in situ. Stages 1–3 are within the breast or regional lymph nodes. Stage 4 is metastatic cancer that has the worst prognosis [25].

Breast cancer cells have receptors on their surface and in their cytoplasm and nucleus. Chemical messengers such as hormones bind to these receptors causing secondary changes in the cells. These receptors include estrogen receptors (ER), progesterone receptors (PR) and HER2 receptors. ER+ cancer cells depend on estrogen for their growth, so they can be treated with antiestrogens (e.g. tamoxifen). Untreated, HER2+ breast cancers are generally more aggressive than HER2- breast cancers [28]. Cancers that do not have any of these three receptor types are called triple-negative. They usually express receptors for other hormones, such as androgens and prolactin [29].

### 7. Prevention of Breast Cancer

Proper control of body weight, drinking less alcohol, physical exercises and breastfeeding are valuable

measures for reduction of the risk of breast cancer. Also, dietary consumption of omega-3 polyunsaturated fatty acids and soya beans appears to reduce the risk [30]. The selective estrogen receptor modulators (such as tamoxifen) reduce the risk of breast cancer but increase the risk of thromboembolism and endometrial cancer. They are recommended only for prevention of breast cancer in women at high risk. The benefit of breast cancer reduction continues for at least five years after stopping these medications [31].

## 8. Management of Breast Cancer

Management of breast cancer depends on many factors including the stage of the cancer and the age of the patient. Breast cancer is usually treated with surgery, which may be followed by chemotherapy or radiation therapy, or both (Figure 1). Hormone receptor-positive cancers are often treated with hormone-blocking therapy over several years. Monoclonal antibodies or other immunomodulators may be given in advanced stages with distant metastasis [32].

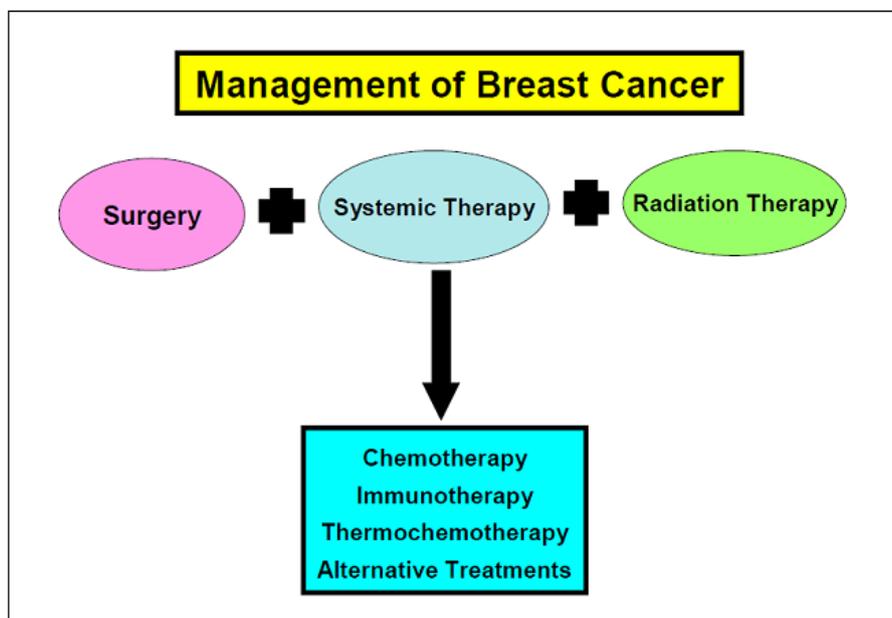


Figure 1. Lines of treatment of breast cancer

### 8.1. Surgery

Depending on the stage and type of the tumor, just lumpectomy may be all that is necessary, or removal of larger amounts of breast tissue may be necessary. Surgical removal of the entire breast is called mastectomy [27]. Before lumpectomy, a needle-localization of the lesion with placement of a guidewire may be performed. However, mastectomy may be the preferred treatment in multifocal cancer, breast previously treated with radiotherapy, large tumor relative to the size of the breast and if the patient has any disease of the connective tissue which may complicate radiotherapy. During the operation, the lymph nodes in the axilla are also considered for removal. If the removed tissue does not have clear margins, further removal of a part of the pectoralis major muscle may be needed [33].

### 8.2. Radiation Therapy

Radiation therapy is an adjuvant treatment for most women after lumpectomy or mastectomy. The purpose of radiation is to reduce the chance of recurrence. Radiation therapy involves using high-energy X-rays or gamma rays that target a tumor or tumor site. This radiation is very effective in killing cancer cells that may remain after surgery or recur where the tumor was removed [34]. Patients undergoing some weeks of radiation therapy usually experience fatigue caused by the healthy tissue repairing itself. Some breast cancer patients develop a suntan-like change in skin color in the exact area being

treated. This darkening of the skin usually returns to normal in one to two months after treatment. Other side effects include muscle stiffness, mild swelling, breast tenderness and lymphedema. After surgery, radiation and other treatments have been completed, many patients notice the affected breast seems smaller. This is due to removal of tissue during the lumpectomy operation [35].

### 8.3. Systemic Therapy

Systemic therapy uses medications to treat cancer cells throughout the body. Systemic treatments include chemotherapy, targeted therapy, immune therapy and hormonal therapy.

#### 8.3.1. Chemotherapy

Chemotherapy may be used before surgery, after surgery, or instead of surgery for inoperable cases. Patients with estrogen receptor positive tumors will receive hormonal therapy after chemotherapy is completed. Typical hormonal treatments include tamoxifen which is given to premenopausal women to inhibit the estrogen receptors, aromatase inhibitors given to postmenopausal women to lower the amount of estrogen in their systems and GnRH-analogues for ovarian suppression in premenopausal women who are at high risk of recurrence [4].

#### 8.3.2. Targeted therapy

Breast cancer targeted therapy uses drugs that block the growth of breast cancer cells in specific ways. For example, in patients whose cancer overexpresses HER2

protein, a monoclonal antibody known as trastuzumab is used to block the activity of the HER2 protein in breast cancer cells. In advanced cases, trastuzumab can be used in combination with chemotherapy to delay cancer growth and improve the patient's survival [36]. It was reported that the use of trastuzumab for up to one year delays the recurrence of breast cancer and improves survival [37].

Other drugs used for targeted therapy include angiogenesis inhibitors (e.g. bevacizumab) that prevent the growth of new blood vessels leading to cutting off the supply of oxygen and nutrients to cancer cells, signal transduction inhibitors which block signals inside the cancer cell that helps the cells to divide, stopping the cancer from growing and antibodies for other hormonereceptors such as androgen receptors and prolactin receptors, which are present in a high proportion of breast cancers [38].

Flaxseed (The highest source of mammalian lignans) was used in animal studies and led to reduction and regression of tumors. Intake of 25 grams of flaxseed daily significantly reduced cell proliferation and increased apoptosis in human breast cancer cells [39]. The preliminary research into flax seeds indicates that flax can significantly change breast cancer growth and metastasis, and enhance the inhibitory effect of tamoxifen on estrogen-dependent breast cancer [40].

### 8.3.3. Immunotherapy

The immune system can fight many types of tumors including breast cancer. A new clinical trial is designed to use oncofetal antigen (OFA) to recruit the patient's own immune system to target and attack the cancer cells to improve patient survival and quality of life. Each patient will receive three monthly injections of the patient's own dendritic cells that have been sensitized to OFA. It is anticipated that once the sensitized cells are injected back into the patient, the patient's T-cells will locate the OFA found on the patient's cancer cells, thereby generating an immune response with killing of the cancer cells and preventing further spread of the disease. Stimuvax is a therapeutic cancer vaccine designed to induce an immune response to cancer cells that express MUC1, a glycoprotein antigen over-expressed on most cancers. Stimuvax is thought to work by stimulating the body's immune system to identify and destroy cancer cells expressing MUC1 [41,42,43].

### 8.3.4. Thermochemotherapy

Medifocus heat treatment added to chemotherapy increased the median tumor shrinkage in the thermochemotherapy arm to 88.4%, while for chemotherapy alone the median tumor shrinkage was 58.8%. For the thermo-chemotherapy treatment arm, almost 80% of breast tumors had a tumor volume reduction of 80% or more, compared to only 20% for the chemotherapy alone [41].

### 8.3.5. Alternative and Adjunctive Treatments

Recent studies have begun treating women suffering from breast cancer with a procedure known as cryoablation. The treatment freezes, then defrosts tumors using small needles so that only the harmful tissue is damaged and ultimately dies. The advantage of this

technique includes alternative to surgery, limiting hospital visits and reducing scarring [41]. Also, traditional herbal medicine were used as adjunctive therapy for treatment of breast cancer. They were proven, in combination with conventional therapy, to improve quality of life and decrease the number of hot flashes per day [44]. Other lines of alternative therapy include group support therapy, cognitive behavioral therapy, cognitive existential group therapy, a combination of muscle relaxation training and guided imagery, thymus extract, transfer factor and melatonin. Encouraging but not fully convincing results were found for melatonin [45].

## 9. Prognosis of Breast Cancer

Prognosis usually depends on many factors including stage, grade, recurrence, age and health of the patient. The stage of the breast cancer is the most important factor. The higher the stage at diagnosis, the poorer the prognosis. The breast cancer grade is assessed by comparison of the breast cancer cells to normal breast cells. The closer to normal the cancer cells are, the slower their growth and the better the prognosis. If cells are not well differentiated, they will appear immature, will divide more rapidly, and will tend to spread [46].

The presence of estrogen and progesterone receptors in the cancer cell is important in guiding treatment. Those who do not test positive for these receptors will not respond to hormone therapy. Also, HER2 status affects the prognosis of the disease. Patients whose cancer cells are positive for HER2 have more aggressive disease and may be treated with trastuzumab, a monoclonal antibody that affects this protein and improves the prognosis [47,48]. Younger women tend to have a poorer prognosis than post-menopausal women due to several factors. Young women may be unaware of the changes that occur in their breasts. So, they are usually at a more advanced stage when diagnosed [49].

## 10. Conclusion

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

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