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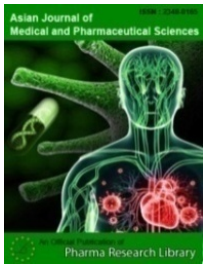

REVIEW ARTICLE

A Review on Treatment of Breast Cancer

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ABSTRACT

Breast cancer in young women is worthy of special attention due to the unique and complex issues that are raised. This article reviews specific challenges associated with the care of younger breast cancer patients, which include fertility preservation, management of inherited breast cancer syndromes, maintenance of bone health, secondary prevention, and attention to psychosocial issues. The most frequent cancer type in females in the Western world is breast cancer, with a lifetime risk of the order of 1/10. Our understanding of the molecular events relating to breast cancer biology and pathogenesis has greatly increased over the last decade. The development of breast cancer involves several types of genes that need to be activated or inactivated in order to promote malignancy. The sequential steps in gene alterations with respect to tumour progression are not clear, and are far less well than what is currently the best example of tumour progression, that is, colon-rectal carcinoma. Still, the large number of alterations that have been identified in breast tumours at the genetic level fit the model of multistep carcinogenesis. Breast cancer is sometimes associated with predisposing mutations in the germ line but is essentially a somatic cell genetic disease. In the present issue of Seminars in Cancer Biology selected topics on breast cancer biology and genetics are reviewed.

Keywords: Breast cancer, Surgery, Radiation therapy, Chemotherapy.

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CONTENTS

1. Introduction

The most frequent point mutations in breast tumours are in the TP53 tumour suppressor gene. But mutations in the TP53 gene occur only in about 30% of breast tumours that is considerably less than the average 50% documented for all tumour types. Magali Olivier and Pierre Hainaut review the 1392 TP53 mutations in breast cancer so far described. Several reports show that TP53 mutations are associated with poorer prognosis but it is not as clear whether these tumours have reduced response to therapy. The p53 protein accumulates in over 50% of breast cancer, partly due to the more stable nature of some of the mutated forms and also because the p53 pathway can be activated in tumour cells, by stabilization of the w.t. p53 protein. The negative regulator of p53, the Mdm2 protein, which can promote p53 degradation, is found over expressed in a fraction of breast cancers, and is presumably an additional mechanism that can turn off the p53 function in the tumour cell. The TP53 differs from several other tumour suppressor genes by the high prevalence of missense mutations. Presumably this gives rise to mutated forms of p53 proteins that can act in a dominant negative manner. As this transcription factor acts as a tetramer, one mutated subunit could be sufficient to affect the function of the protein complex. In breast cancer 30% of TP53 mutations cluster at eight hotspot codons and a similar profile of TP53 mutations is detected as in other cancer types, except that there is a slightly lower frequency of transversions and slightly higher frequency of transitions. The transversions are generally more common in cancers in which carcinogens play an important role. The mutation pattern in the TP53 gene is different in Western countries compared with Japan, particularly in individuals diagnosed with breast cancer under 45 years of age, and there are also reports on higher prevalence of small deletions in specific regions of the USA. These differences in the TP53 mutations spectrum support the hypothesis that a fraction of breast cancer mutations may be induced in response to exposure to environmental carcinogens. In all, 196 germline mutations have been detected in the TP53 gene and 164 of them exist in cancer families. Breast cancer is the most frequent type of cancer in patients with inherited TP53 mutation, and mutation of one allele can predispose to early disease. The pattern of germline mutations in comparison with sporadic mutations show increased frequency of transitions at CpG sites and reduced frequency of transversions at non-CpG sites. This could possibly be explained by a specific endogenous mutagenic process that acts in the germline.

Breast Cancer:

Breast cancer is a disease in which cells in the breast grow out of control. There are different kinds of breast cancer. The kind of breast cancer depends on which cells in the breast turn into cancer.

Breast cancer can begin in different parts of the breast. A breast is made up of three main parts: lobules, ducts, and connective tissue. The lobules are the glands that produce milk. The ducts are tubes that carry milk to the nipple. The connective tissue (which consists of fibrous and fatty tissue) surrounds and holds everything together. Most breast cancers begin in the ducts or lobules.Breast cancer can spread outside the breast through blood vessels and lymph vessels. When breast cancer spreads to other parts of the body, it is said to have metastasized.

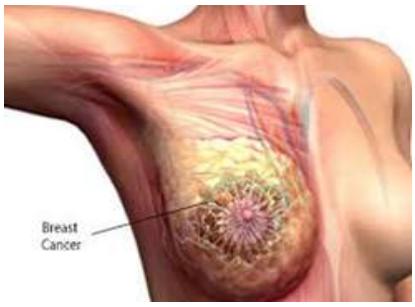

Fig 1: Breast cancer

2. Pathophysiology

Breast cancer, like other cancers, occurs because of an interaction between an environmental (external) factor and a genetically susceptible host. Normal cells divide as many times as needed and stop. They attach to other cells and stay in place in tissues. Cells become cancerous when they lose their ability to stop dividing, to attach to other cells, to stay where they belong, and to die at the proper time. Normal cells will commit cell suicide (programmed cell death) when they are no longer needed. Until then, they are protected from cell suicide by several protein clusters and pathways. One of the protective pathways is the PI3K/AKT pathway; another is the RAS/MEK/ ERK pathway. Sometimes the genes along these protective pathways are mutated in a way that turns them permanently "on", rendering the cell incapable of committing suicide when it is no longer needed. This is one of the steps that cause cancer in combination with other mutations. Normally, the PTEN protein turns off the PI3K/AKT pathway when the cell is ready for programmed cell death. In some breast cancers, the gene for the PTEN protein is mutated, so the PI3K/AKT pathway is stuck in the "on" position, and the cancer cell does not commit suicide. Mutations that can lead to breast cancer have been experimentally linked to estrogen exposure. Additionally, G-protein coupled estrogen receptors have been associated with various cancers of the female reproductive system including breast cancer. Abnormal growth factor signaling in the interaction between stromal cells and epithelial cells can facilitate malignant cell growth. In breast adipose tissue, over expression of leptin leads to increased cell proliferation and cancer. In the United States, 10 to 20 percent of people with breast cancer and people with ovarian cancer have a first- or second-degree relative with one of these diseases. The familial tendency to develop these cancers is called hereditary breast–ovarian cancer syndrome. The best known of these, the *BRCA* mutations, confer a lifetime risk of breast cancer of between 60 and 85 percent and a lifetime risk of ovarian cancer of between 15 and 40 percent. Some mutations associated with cancer, such as *p53*, *BRCA1* and *BRCA2*, occur in mechanisms to correct errors in DNA. These mutations are either inherited or acquired after birth. Presumably, they allow further mutations, which allow uncontrolled division, lack of

attachment, and metastasis to distant organs. However, there is strong evidence of residual risk variation that goes well beyond hereditary *BRCA* gene mutations between carrier families. This is caused by unobserved risk factors. This implicates environmental and other causes as triggers for breast cancers. The inherited mutation in *BRCA1* or *BRCA2* genes can interfere with repair of DNA cross links and DNA double strand breaks (known functions of the encoded protein). These carcinogens cause DNA damage such as DNA cross links and double strand breaks that often require repairs by pathways containing BRCA1 and BRCA2. However, mutations in *BRCA* genes account for only 2 to 3 percent of all breast cancers. Levin *et al.* say that cancer may not be inevitable for all carriers of *BRCA1* and *BRCA2* mutations. About half of hereditary breast–ovarian cancer syndromes involve unknown genes. GATA-3 directly controls the expression of estrogen receptor (ER) and other genes associated with epithelial differentiation, and the loss of GATA-3 leads to loss of differentiation and poor prognosis due to cancer cell invasion and metastasis.

Fig 2: Pathophysiology of breast cancer

3. Causes and Symptoms of Breast Cancer

After puberty, a woman's breast consists of fat, connective tissue, and thousands of lobules. These are tiny glands that produce milk for breastfeeding. Tiny tubes, or ducts, carry the milk toward the nipple. Cancer causes the cells to multiply uncontrollably. They do not die at the usual point in their life cycle. This excessive cell growth causes cancer because the tumor uses nutrients and energy and deprives the cells around it.Breast cancer usually starts in the inner lining of milk ducts or the lobules that supply them with milk. From there, it can spread to other parts of the body.

Fig 3: Causes of breast cancer

Symptoms of Breast Cancer

The first symptoms of breast cancer usually appear as an area of thickened tissue in the breast or a lump in the breast or an armpit.

Other symptoms include:

- pain in the armpits or breast that does not change with the monthly cycle
- pitting or redness of the skin of the breast, similar to the surface of an orange
- a rash around or on one of the nipples
- discharge from a nipple, possibly containing blood
- a sunken or inverted nipple
- a change in the size or shape of the breast
- peeling, flaking, or scaling of the skin on the breast or nipple

Most breast lumps are not cancerous. However, women should visit a doctor for an examination if they notice a lump on the breast.

Fig 4: Symptoms of breast cancer

4. Risk Factors of Breast Cancer

The exact cause of breast cancer remains unclear, but some risk factors make it more likely. It is possible to prevent some of these risk factors.

1. Age:

The risk of breast cancer increases with age. At 20 years, the chance of developing breast cancer in the next decade is 0.06%. By the age of 70 years, this figure goes up to 3.84%.

2. Genetics:

If a close relative has or has had breast cancer, a person's chance of developing breast cancer increases.

Women who carry the BRCA1 and BRCA2 genes have a higher chance of developing breast cancer, ovarian cancer, or both. People can inherit these genes from their parents. TP53 is another gene with links to increased breast cancer risk.

3. A history of breast cancer or breast lumps:

Women who have previously had breast cancer are more likely to have it again than those who have no history of the disease. Having some types of noncancerous breast lump increases the chance of developing cancer later on. Examples include atypical ductal hyperplasia or lobular carcinoma in situ.

4. Dense breast tissue:

Women with more dense breasts are more likely to receive a diagnosis of breast cancer.

5. Estrogen exposure and breastfeeding:
Breastfeeding for over 1 year appears to reduce the risk of breast cancer. Extended exposure to estrogen appears to increase the risk of breast cancer.
This could be due to a person starting their periods earlier or entering menopause at a later than average age. Between these times, estrogen levels are higher. Breastfeeding, especially for over 1 year, appears to reduce the chance of developing breast cancer. This is possibly due to the drop in estrogen exposure that follows pregnancy and breastfeeding.
6. Body weight:
Women who become overweight or develop obesity after menopause may also have a higher chance of developing breast cancer, possibly due to increased estrogen levels. High sugar intake may also be a factor.
7. Alcohol consumption:
A higher rate of regular alcohol consumption appears to play a role in breast cancer development.
According to the National Cancer Institute (NCI), studies have consistently found that women who consume alcohol have a higher risk of breast cancer than those who do not. Those who drink moderate to heavy levels of alcohol have a higher risk than light drinkers.
8. Radiation exposure:
Undergoing radiation treatment for a different cancer may increase the risk of developing breast cancer later in life.
9. Hormone treatments:
According to the NCI, studies have shown that oral contraceptives may slightly increase the risk of breast cancer. According to the ACS, studies have found that hormone replacement therapy (HRT), breast cancer.

Fig 5: Risk factors of breast cancer

5. Diagnosis of Breast Cancer

The following tests may be used to diagnose breast cancer or for follow-up testing after a breast cancer diagnosis.
Imaging tests
Imaging tests show pictures of the inside of the body. The following imaging tests of the breast may be done to learn more about a suspicious area found in the breast during screening. In addition to these, there are other newer types of tests that are being studied.
Diagnostic mammography: It is similar to screening mammography except that more pictures of the breast are taken. It is often used when a woman is experiencing signs, such as a new lump or nipple discharge. Diagnostic mammography may also be used if something suspicious is found on a screening mammogram.

- **Ultrasound:** An ultrasound uses sound waves to create a picture of the breast tissue. An ultrasound can distinguish between a solid mass, which may be cancer, and a fluid-filled cyst, which is usually not cancer.
- **MRI:**
  An MRI uses magnetic fields, not x-rays, to produce detailed images of the body. A special dye called a contrast medium is given before the scan to help create a clear picture of the possible cancer. This dye is injected into a patient's vein. A breast MRI may be used after a woman has been diagnosed with cancer to check the other breast for cancer or to find out how much the disease has grown throughout the breast. Breast MRI is also a screening option, along with mammography, for some women with a very high risk of developing breast cancer.

Biopsy:
A biopsy is the removal of a small amount of tissue for examination under a microscope. Other tests can suggest that cancer is present, but only a biopsy can make a definite diagnosis. A pathologist then analyzes the sample(s). A pathologist is a doctor who specializes in interpreting laboratory tests and evaluating cells, tissues, and organs to diagnose disease. There are different types of biopsies, classified by the technique and/or size of needle used to collect the tissue sample.

- Fine needle aspiration biopsy: This type of biopsy uses a thin needle to remove a small sample of cells.
- Core needle biopsy: This type uses a wider needle to remove a larger sample of tissue. This is usually the preferred biopsy technique for finding out whether an abnormality on a physical examination or an imaging test is cancer. Local anesthesia, which is medication to block pain, is used to lessen a patient's discomfort during the procedure.
- **Surgical biopsy:** This type removes the largest amount of tissue. Because surgery is best done after a cancer diagnosis has been made, a surgical biopsy is usually not the recommended way to diagnose breast cancer. Most often, non-surgical core needle biopsies are recommended to diagnose breast cancer.
- **Image-guided biopsy:**
  During this procedure, a needle is guided to the location with the help of an imaging technique, such as mammography, ultrasound, or MRI. A stereotactic biopsy is done using mammography to help guide the needle. A small metal clip is usually put into the breast to mark where the biopsy sample was taken, in case the tissue is cancerous and more surgery is needed. This clip is usually titanium so it will not cause problems with future imaging tests, but check with your doctor before you have any imaging tests. An image-guided biopsy can be done using a fine needle, core, or vacuum-assisted biopsy (see above), depending on the amount of tissue being removed.

Imaging tests may also be used to find the best place to take a biopsy sample of a lump that can be felt.

- Sentinel lymph node biopsy: This procedure is a way to find out if there is cancer in the lymph nodes near the breast.

Analyzing the biopsy sample:

Analyzing the sample(s) removed during the biopsy can help your doctor learn about specific features of a cancer that help determine treatment options.

- **Tumor features:** Examination of the tumor under the microscope is used to determine if it is invasive or in situ, ductal or lobular, and whether the cancer has spread to the lymph nodes. The margins or edges of the tumor are also examined and their distance from the tumor is measured, which is called margin width.
- **ER and PR:** Testing for ER and PR helps determine both the patient's risk of recurrence and the type of treatment that is most likely to lower the risk of recurrence. ER and PR are often measured for DCIS as well. Generally, hormonal therapy works well for ER-positive and/or PR-positive cancers.
- **HER2:** The HER2 status helps determine whether drugs that target the HER2 receptor, such as trastuzumab (Herceptin, Herzuma, Ogivri, and Ontruzant), might help treat the cancer. This test is only done on invasive cancers. ASCO and CAP recommend that HER2 testing is done when you are first diagnosed with an invasive breast cancer. If the cancer has spread to another part of your body or comes back after treatment, testing should be done again on the new tumor or areas where the cancer has spread, especially if results would influence your treatment options.
- HER2 tests are usually clearly positive or negative, meaning that your cancer has either a high or low level of HER2. If your test results are not clearly positive or negative.If the cancer is HER2 positive, HER2-targeted therapy may be a recommended treatment option for you. If the cancer is HER2 negative, HER2-targeted therapy is not a treatment option for you, and your doctor will give you other options for treating the breast cancer.

6. Treatment of Breast Cancer

Some treatments remove or destroy the disease within the breast and nearby tissues, such as lymph nodes. These include:

Surgery:

To remove the whole breast, called a mastectomy, or to remove just the tumor and tissues around it, called a lumpectomy or breast-conserving surgery. There are different types of mastectomies and lumpectomies.

Radiation Therapy:

Radiation therapy which uses high-energy waves to kill cancer cells. Radiation therapy and invasive breast cancer

After lumpectomy:

Radiation therapy is usually recommended after lumpectomy.

Radiation therapy can lower the risk of:

- Breast cancer recurrence
- Breast cancer death

After mastectomy:

Many women who have a mastectomy don't benefit from radiation therapy.

However, in some cases, radiation therapy is used after mastectomy to treat the chest wall and lymph nodes. These can include the lymph nodes in the underarm area (axillary nodes), around the collarbone or near the breastbone (internal mammary nodes).

Other treatments destroy or control cancer cells all over the body.

Chemotherapy:

Chemotherapy uses drugs to kill cancer cells. As these powerful medicines fight the disease, they also can cause side effects, like nausea, hair loss, early menopause, hot flashes, and fatigue

After lumpectomy:

Radiation therapy is usually recommended after lumpectomy.Radiation therapy can lower the risk of:

- Breast cancer recurrence
- Breast cancer death

After mastectomy:

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Table 1: Drugs used in Chemo therapy

Drugs	Brand name
Capecitabine	Xeloda
Carboplatin (C)	Paraplatin
Cyclophosphamide (C)	Cytoxan
Docetaxel (T)	Taxotere
Doxorubicin (A)	Adriamycin
Epirubicin (E)	Ellence
Methotrexate (M)	Various brand names
Paclitaxel (T)	Taxol

Hormone therapy:

Uses drugs to prevent hormones, especially estrogen, from fueling the growth of breast cancer cells. Some breast cancer cells need estrogen and/or progesterone (female hormones produced in the body) to grow. When these hormones attach to special proteins called hormone receptors, the cancer cells with these receptors grow.

Hormone therapy drugs slow or stop the growth of hormone receptor-positive tumors by preventing the cancer cells from getting the hormones they need to grow.

All tumors are checked for hormone receptors. A pathologist determines the hormone receptor status by testing the tumor tissue removed during a biopsy

- **Hormone receptor-positive:** (estrogen receptor-positive/progesterone receptor-positive) tumors express (have a lot of) hormone receptors.

- **Hormone receptor-negative:** (estrogen receptor-negative/progesterone receptor-negative) tumors do not express (have few or no) hormone receptors.

Hormone therapies are only used to treat hormone receptor-positive breast cancers. Most breast cancers are hormone receptor-positive. Hormone therapy drugs slow or stop the growth of hormone receptor-positive tumors in a few ways:

- Some hormone therapies, such as tamoxifen, attach to the receptor in the cancer cell and block estrogen from attaching to the receptor.
- Others, such as aromatase inhibitors and ovarian suppression, lower the level of estrogen in the body so the cancer cells can't get the estrogen they need to grow.
- Medicinesinclude tamoxifen (Nolvadex, Soltamox)forwomenincluding anastrozole (Arimidex), exemestane (Aromasin), and letrozole (Femara) for postmenopausal women. Side effects can include hot flashes and vaginal dryness. Some types of this therapy work by stopping the ovaries from making hormones, either through surgery or medication. Fulvestrant (Faslodex) is an injection that keeps estrogen from attaching to cancer cells.

Targeted Therapy:

Such as lapatinib (Tykerb), pertuzumab (Perjeta), and trastuzumab (Herceptin). These medicines prompt the body's immune system to destroy cancer. They target breast cancer cells that have high levels of a protein called HER2. Palbociclib (Ibrance) work by blocking a substance that promotes cancer growth. Along with an aromatase inhibitor, palbociclib and ribociclib are for postmenopausal women with certain types of advanced cancer. Abemaciclib and palbociclib are sometimes used with the hormone therapy fulvestrant (Faslodex). A new class of drugs called PARP (poly ADP ribose polymerase) inhibitors targets an enzyme that feeds cancer cells. PARP inhibitors include talazoparib (Talzenna) and talazoparib (Talzenna).

- In some cases, treatment with chemotherapy, HER2-targeted therapy or hormone therapy may be given before breast surgery. When treatment is given before surgery, it's called neoadjuvant therapy or preoperative therapy.
- Neoadjuvant chemotherapy and hormone therapy drugs are the same as those used after surgery (called adjuvant therapy).
- Before neoadjuvant therapy begins, you will have a needle biopsy to remove a small amount of tumor tissue.
- A radio-opaque clip is often placed in the tumor bed so the tumor can be found later when you have surgery. (This clip will be removed during surgery.)
- Tests on the biopsy tissue confirm your diagnosis and identify tumor characteristics, such as hormone receptor status and HER2 status. These factors determine the type(s) of neoadjuvant therapy that will offer the most benefit.

Neoadjuvant therapy:

Treatment plan includes chemotherapy; neoadjuvant chemotherapy may be an option as a first treatment.

Chemotherapy has the same effectiveness whether it's given before surgery or after surgery. The timing of chemotherapy around surgery does not affect survival.

However, for some women, neoadjuvant chemotherapy can change their surgical options. Neoadjuvant chemotherapy may be able to shrink a larger tumor enough so lumpectomy plus radiation therapy becomes an option instead of mastectomy. Neoadjuvant chemotherapy may also be given to women who have enlarged lymph nodes in the underarm area (due to the spread of breast cancer to these lymph nodes). This makes the surgery to remove these lymph nodes easier. Most tumors respond to neoadjuvant chemotherapy. If a tumor does not respond to one chemotherapy drug regimen, the combination of drugs may be changed or it may be best to proceed with surgery.

Types of Neoadjuvant chemotherapy regimens:

- Neoadjuvant chemotherapy regimens are the same as the standard regimens used after surgery. Most are anthracycline- or taxane-based therapies.
- For HER2-positive tumors, neoadjuvant therapy usually includes a combination of the HER2-targeted therapy drugs trastuzumab (Herceptin) and pertuzumab (Perjeta).
- Treatment plan includes chemotherapy; neoadjuvant chemotherapy may be an option as a first treatment.
- Chemotherapy has the same effectiveness whether it's given before surgery or after surgery. The timing of chemotherapy around surgery does not affect survival.
- However, for some women, neoadjuvant chemotherapy can change their surgical options. Neoadjuvant chemotherapy may be able to shrink a larger tumor enough so lumpectomy plus radiation therapy becomes an option instead of mastectomy.

Neoadjuvant chemotherapy may also be given to women who have enlarged lymph nodes in the underarm area (due to the spread of breast cancer to these lymph nodes). This makes the surgery to remove these lymph nodes easier. Most tumors respond to neoadjuvant chemotherapy. If a tumor does not respond to one chemotherapy drug regimen, the combination of drugs may be changed or it may be best to proceed with surgery.

4. Conclusion

The committee believes that the IP represents a new and imaginative concept in planning and monitoring a research grants program. By functioning as a second-tier (programmatic) review and council, and reporting to contractors and predominantly nonscientific administrators within the Army, the IP wields considerable power in deciding investment strategies and funding policy. The unquestionable success of the IP is the result of the high level of dedication and professional excellence of its members. The committee is concerned that it may be difficult to continue to recruit individuals with both the

expertise and the level of commitment needed to sustain the wide range of current responsibilities of the IP. The committee believes that it is important to maintain the current high status within the research community that serving on the IP confers. In part, this will be sustained by continuing to accord a high level of responsibility to the Panel. However, the workload of individual IP members should be reduced where possible. For example, if the program's funding is stabilized, tasks such as development of program announcements and proposal formats, orientation of executive secretaries and development of new investment strategies may not need to be revisited by the IP every year. However, the program's unique flexibility should be protected as the program matures.

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