Original Article

Etiology Of Breast Cancer

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Abstract

Breast cancer is a fusion, diverse, and composite disease of women. There is no sole cause of breast cancer. The Origin of breast cancer are not perfectly known. However, there are many predisposing factors known to affect possibility of developing breast cancer. The risk of breast cancer has been compatible associated with age, a family or genetically history of breast cancer, History of early menarche, Delayed age first pregnancy, short period or no breastfeeding, and late menopause, Prolonged period of hormonal therapy (HT), alcohol consumption, sedentary lifestyle, exposure to ionizing radiation like X-rays, and genetic predisposition. Mutations in inherited high penetrance genes can cause only 5–10% of all types of breast cancers.

Keywords:- Breast cancer; predisposing factors; history; genetic; Mutations

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Introduction

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INTRODUCTION

Breast cancer is a disorder of breast in which cells in the breast grow rapidly and became uncontrolled. Breast cancer is classified in many ways based on breast cells or tissue convert into cancerous cell.

Breast cancer can originate in lobules, ducts, and connective tissue. Ducts or lobules of breast are mainly affected by cancer. Metastasis of breast cancer can take place through blood vessels and lymph nodes.

The most common type of breast cancer are Invasive ductal and lobular carcinoma.

- **Invasive ductal carcinoma:-** Carcinoma begin in the ducts and then grow rapidly and spread to other parts of the breast tissue. Through metastasis it can spread to other part of body.
- **Invasive lobular carcinoma.** Originates in the lobules of breast and advance to other organs and close by through invasion and metastasis.

Infrequent or other types of breast carcinoma: These are as following

Inflammatory breast carcinoma

This types of carcinoma begins with inflammation or injury of breast. As a result of inflammation they become tender, swollen, red and itchy. Inflammatory breast cancer at first be diagnosed as a breast infection or mastitis due to similarities of clinical manifestations. Through antibiotics breast infection will resolve but breast cancer cannot treat. If it is not treated by antibiotics within 10 days indicates sign of breast cancer.

This types of breast cancer is rare, often starts in the soft tissues of the breast and causes the blocked the lymph node vessels in the breast. As a result of cancer, the breast may become inflamed, and shows the sign and symptoms inflammation.

Metastatic breast cancer

When breast cancer spread to other organs like lung, liver, heart, brain and bone through metastasis by blood or lymph nodes its known as Metastatic breast cancer. It is also known as advanced breast cancer or stage 4 breast cancer. Metastases from breast cancer mostly found in the armpit lymph nodes, or they can circulate anywhere in the body through circulation. After surgery even small microscopic tumour emboli remains in circulation can cause return of cancer. Recurrence of breast cancer depends on immune system of patient.

Male breast cancer

Male breast cancer occurs when abnormal malignant cells starts growing in the tissues of the breast. Prevalence of breast cancer is about 1 percent of all breast cancers occur in men. Each year approximately 2000 men are diagnosed with breast cancer. Most common age of cancer of breast in man ranges from 60 to 70 years. This is uncommon because male breasts are not influenced by female hormones. They are also protected by hormones secreted by testicles. Gynecomastia (enlargement of breast in male) the most common male breast disorder. Gynecomastia is not a form of cancer but rarely, it can be is due to a tumour. Any changes or enlarged lumps should be examined or evaluated by doctor.

Paget's disease of the breast

It is a rare types of cancer that causes distinct structural changes on the nipple. It is accounting less than 3% of all type of breast cancers. In 1874 it is discovered by English surgeon Sir James Paget.

Medullary ductal carcinoma: It is called “medullary” because, microscopic study reveals that it appears like a medulla of brain. It may develop at any maturity, but typically common in women in between 40 to 50. BRCA1 gene mutation women have more diagnosed with Medullary Breast carcinoma. Medullary ductal cancer is rare and accounts for 3-5% of breast cancers.

Mucinous ductal carcinoma: Mucinous ductal carcinoma is also called colloid carcinoma, it affects Menopausal women.

Papillary ductal carcinoma: It is seen in postmenopausal women and accounting less than 1 percent of Invasive breast cancers. Most papillary carcinomas are invasive in nature and are treated like invasive ductal carcinoma.

Tubular ductal carcinoma: They account less than 2 percent of breast cancer diagnoses. Tubular breast cancer evolve in the milk duct, and metastasises to surrounding tissues of duct. This type is more common in women older than 50.

Etiology of breast cancer

Incidence of breast carcinoma is 1 in 10 of new diagnoses. Worldwide it is the second leading cause of death from cancer in females. Exact cause of breast cancer is unknown, certain risk factors are known, no common etiologic or causative factors being investigated for breast cancer. A woman's age, genetic factors, family history, personal health history, and diet all contribute to breast cancer risk.

To understand easily risk or possible factors for breast cancer can divide into two categories first Controllable and second uncontrollable risk factors.

Controllable risk factors for breast cancer:

Controllable risk factors are behaviours and exposures that can raise or lower a person’s risk of breast cancer, anyone can take measures to change them or modify through the advice of healthcare provider.

Smoking: - The most recent evidence has suggested a potentially casual role for active smoking and breast cancer, particularly for long-term heavy smoking and smoking initiation at an early age. Recent studies suggest that smoking plays role in breast cancer somehow.

Alcohol consumption: - Breast cancer risk increases with the amount of alcohol consumed by women. A research study reveals that, women who consume alcohol daily have 20 % higher risk of developing breast cancer than women who do not consume alcohol at all.

Alcohol can increase levels of estrogen and other hormones associated with hormone-receptor-positive breast cancer. Alcohol also may increase breast cancer risk by damaging DNA in cells.

A meta-analysis that combined the results of 98 studies found women who drank alcohol were 11 percent more likely than non-drinkers to get breast cancer.

Obesity: - Being overweight or obese is a risk factor for breast cancer. A body mass index over 25 have a greater risk of developing breast cancer in comparison to women who maintain a healthy weight, especially after menopause.

Several studies reveal that a significantly stronger association is obesity and increased body mass index and higher incidence of breast cancer among women. In obese women estrogen level raise due to excessive aromatization activity of the adipose tissue, over expression of pro-inflammatory cytokines, insulin resistance, hyper activation of insulin-like growth factors pathways, adipocyte derived adipokines, hyperlipidemia and excessive oxidative stress contribute to the development of breast cancer. In lean women with history of hormone replacement therapy have greater risk of developing breast cancer and in postmenopausal women those who are not taking hormones suppliments are at the risk of breast cancer. Predictor for breast cancer general obesity is known factor. In addition, excess cholesterol leads to accelerated.

Pregnancy: Having children has a complex effect on breast cancer risk. Overall, in the long term, Pregnancy reduces the risk of breast cancer. Research suggests a strong association between pregnancy and breast cancer has been well established. Although early age pregnancy is considered generally protective against breast cancer, this protection is deferred. Nevertheless, the period immediately subsequent to pregnancy is characterized by a risk of breast cancer development.

Breastfeeding: It reduces risk of developing breast carcinoma, especially if someone did it for a year or longer. Breast cancer reduction is just one of many benefits associated with breastfeeding. The American academy of pediatrics and many other associations recommends breastfeeding for about the first six months of life, then continuing to breastfeed, supplementing with appropriate foods, for one year or longer.

Researchers found that if a woman breastfed their baby for 12 months her risk of breast cancer decreased by 4.3%. The study compared mothers who breastfed to their babies and who didn't. It also found the 12-month time period could be with either one child or as the total for several children.

Low physical activity: Physical activity or exercise is associated with decreased breast cancer risk through several interlinked biological channel might imply adiposity, gonadal hormones, insulin resistance, adipokines, and chronic or old inflammation.

Worldwide many research studies conducted to identify relationship between physical exercise and risk of breast cancer in women. These studies, suggest that the average breast cancer risk reduction, when comparing to the less physically active women, was 25 percent. It is also reveals that physical activity is helpful in reduction of breast cancer in women of all races.

It is also observed in research that a reduced risk of breast cancer in women who were more physically active at their young age than their peers at ages 10-15 years (around the age of menarche). A reduced risk of breast cancer found as a result of physical activity during these years.

Women those who have larger amounts of abdominal fat, with a lack of physical activity might increase the risk of breast cancer.

Current research evidence concludes that regular physical activity or exercise after diagnosis of breast cancer may mitigate common side effects of breast cancer chemotherapy and surgical treatment, like weakness, mood disorder, impaired quality of life, muscular weakness, appetite, and weight gain.

Non-controllable risk factors for breast cancer

Gender: breast cancer is common in women than men although men do get breast cancer. Men might develop breast cancer, but this is about 100 times more usual among women than men**.** Human breasts in both genders have similar anatomical structures like nipples, adipose tissue, breast cells and ducts. Both genders also are at the same risk for breast cancer. Men and women might have inherited mutations in their BRCA1 and BRCA2 genes and both genders produce the hormone estrogen, which may increase the risk of developing breast cancer.
Many study demonstrated various gender-specific differences. The breast cancer in both genders (men & women) appears more alike than different.

- Approximately 80 percent breast cancers in men are hormone receptor positive.
- Breast cancer of both genders (men and women) can treated by chemotherapy, radiation, surgical and hormonal therapy.
- When a man are born with two X chromosomes condition is called Kline felter syndrome, in this disease men have produce excess amount of estrogen which may increase the risk of breast cancer.
- Men and women breast cancers have similar clinical manifestations, like a tumor or mass felt on the breast, enlargement of breast in manner of size and shape, sign of inflammation over irritated skin and changes in the nipple can similarly observed.

Being a women place a greater risk for developing breast cancer. Men can also develop breast cancer, but risk of developing breast cancer is less than 1% of all new breast cancer cases.
The major reasons for rate of breast cancer, difference in men and women are as follows:

- By the age 14 women's breast starts developing, and takes 3-4 years to complete development but in men it's uncommon for breasts to fully form and they are just fatty tissue mostly not formed breast glands.
- Once fully formed women breast cells are very immature and become highly active during a woman's first full-term pregnancy. A women's immature, breast cells are very responsive or sensitive to estrogen and other sex hormones, including hormone anarchist in the environment.
- Due to inactivity of men's breast cells they have extremely low levels of estrogen hormone which protect them from breast cancer.

Breast cancer is much more common in women than in men due to highly responsive breast cells during extra sensitive period of breast development by hormonal stimulation.

- **Personal history of breast cancer.** Breast cancer can develop again if a women who had already history of breast cancer in the past. Positive history of breast cancer put a client on greater risk of developing breast cancer again. The new breast cancer can develop in the same breast as the first cancer or in the other breast. Women who had history of DCIS (ductal carcinoma in situ) or LCIS (lobular carcinoma in situ) have a greater risk of developing a second breast cancer. A woman who has had breast cancer in 1 breast has a higher risk of developing a new cancer in other breast. Metastasis is also common in these type of breast cancer.
- **Breast density:** Women who have dense breast are higher risk of developing breast cancer. In dense breasts have plenty of glands and fibrous tissue in comparison of fat breasts but normal anatomically it is combination of fatty, fibrous and glandular tissue. Risk of developing breast cancer in a woman who is having breast cancer is 1.5 to 2%. It can also make it difficult to see tumors in mammograms which are diagnosis of breast cancer. Research is examining whether breast density may be modifiable by changing women's hormones or diet. One medication Tamoxifen have been demonstrated positive results in reduction of breast density and can use as a prophylactic drug.
- **Advance age.** Aging is a factor. A majority of new breast cancer diagnoses come after the age of 55. Risk of breast cancer goes up as age advances. About 77% of women diagnosed with breast cancer each year are over 50, and more than 40% are 65 and older.

Table 1.1 shows age and percentage of risk of breast cancer

Age in years	Percentage of risk of breast cancer
40-50	1-2%
Above 50	77%
65 or Over	40%

- **Reproductive risk factors can be classified into increased or decreased factors**
- Reproductive factors which can increase the risk factors are early **Menarche (**getting menstrual period before age 12**), Nulliparity** (A woman having no children), **late age at first pregnancy** (having first child after 30.)**, late menopause** (entering menopause after age 55)etc.
- Early and first full-term pregnancy, longer duration of breast feeding(greater than 6 months), increasing number of births, history of preeclampsia,can reduce the risk of developing breast cancer.
- In addition to well-established reproductive and lifestyle risk factors such as early age at menarche and HRT intake, there is a strong risk in relation to family history of breast cancer, with a two fold increase in risk of developing the disease for women with breast cancer in their first-degree family, and a larger increase in risk among women with a first-degree relative diagnosed before age 50 compared with after age 50 years

- **Exposure to radiation:** A woman who exposed in radiation over chest or breast during treatment or diagnosis of chest disorders by fluoroscopy X-rays. Exposure to radiation therapy at early age or about 30 may increases risk of breast cancer. Hodgkin lymphoma treatment by Mantle-field radiation therapy have four times greater risk of breast cancer over the next 20 to 30 years.Exposure to ionizing radiation like X-ray at a young age may increase a woman's risk of developing breast cancer. For example, therapeutic radiation to the chest treatment for Hodgkin's lymphoma may raise breast cancer risk in both breasts.

- **High socio-economic status:** Developing of breast cancer risk is slightly greater for women with higher incomes or socio-economic status. Breast cancer among high socio economic women may be because of sedentary lifestyle factors like alcohol consumption, smoking, dietary habits, lack of physical activity and having children later in life or having fewer children or no breast feeding.

- **Serum estradiol level:** Estradiol is the main form of estrogen circulating in the women body. 'Serum estradiol' refers to the amount of estradiol in the blood. A women's serum estradiol level can be measured with a simple blood test. In postmenopausal women, higher hormone levels in the blood have been associated with an increased risk of breast cancer. So a vigilant woman can go through serum estradiol test periodical for screening of breast cancer risk.

- **Family history of breast cancer,** Family history is a major risk factor for breast cancer; approximately 5-10 percent cases of breast cancer are associated with a family history. Breast cancer may includes having a first degree relative (eg. mother, sister, daughter, father, brother, son) with breast cancer poses a higher risk for individual. If someone have more than one relative on either side of family with breast cancer, than have a greater risk.

Breast cancer might run in the family if someone has following of these situations:

- Breast cancer diagnosed one or more in women at age 45 or younger
- Breast cancer diagnosed one or more in women before age 50 with an additional family history of other types of cancer, e.g. ovarian cancer, colonic cancer, prostatic cancer, and pancreatic cancer etc.
- There is family history of breast cancer and ovarian cancers in more than one generation on one side of the family, such as history of breast cancer having both a grandmother and an aunt on the father's side of the family who were both or one diagnosed breast cancer or other cancer.
- A woman is diagnosed with a second breast cancer in the same in family or the other breast cancer or has both breast cancer and ovarian cancer.
- A male or men relative in family is diagnosed with breast cancer.
- One close relative at age 50 or younger who was diagnosed with breast cancer or colonic, ovarian, prostate, and pancreatic cancer.

- **Genetic mutations related to certain types of breast cancer.** Approximately 5% to 10% of breast cancers are thought to be hereditary of all cancers result from autosomal transmission of a mutated gene**.** In terms of genetic mutations, these include changes to genes like BRCA1 and BRCA2.
- Due to DNA damage and genetic mutations or changes breast cancer can develops it can be also influenced by exposure to estrogen.
- The most common cause of hereditary breast cancer is an inherited mutation in the BRCA1 or BRCA2 gene. In normal cells, these genes help make proteins that repair damaged DNA. Mutated versions of these genes can lead to abnormal cell growth, which can lead to cancer.
- Based on researches experts have suggested the levels of breast cancer risk that may be related gene mutation. These levels of genetic risk are generally classified as:

- **High Risk:** greater than 50% in Lifetime breast cancer risk is estimated as high risk.

- **Moderate to High risk:** Lifetime breast cancer risk estimates from 25% to over 50% as moderate to high risk.

- **Moderate risk of** breast cancer risk is estimated at about 25% to 50%.

- **Uncertain risk:** There is no sufficient evidence from research studies which shows any link between mutation and breast cancer risk.

However, these risks can be reduced through, maintaining a healthy diet and weight, exercising regularly physical activity, limiting alcohol eating antioxidants and balanced diet, and quitting smoking.

- **Familial cancers associated with breast cancer Table 1.2**

Type of cancer	Manifestation	Genetic mutation	Mode of inheritance
Breast/ ovarian syndrome	Breast cancer , Ovarian cancer, Prostatic cancer, or Colonic cancer	BRCA1	Autosomal dominant
Site specific breast cancer	Breast cancer (Male and female), Ovarian cancer	BRCA2	Autosomal dominant

- **Having already had breast cancer.** The risk is higher a women if she have already had breast cancer and other types of benign breast disorder such as lobular carcinoma in situ, ductal carcinoma in situ, or atypical hyperplasia.

- **Exposure to diethylstilbestrol (DES).** In United States during 1940-1971 diethylstilbestrol was administered to some pregnant women. Diethylstilbestrol is a synthetic form of the female hormone estrogen. If a woman have taken diethylstilbestrol in her lifetime or a woman's mother took this drug, have a higher risk of developing breast cancer.

- Most research suggests women who took diethylstilbestrol appear to have an increased risk of breast cancer. The risk of breast cancer in diethylstilbestrol exposed mothers is about 30% higher than the risk of women who have not been exposed to this drug.

- **Race and ethnicity:** Black and white women have the greater risk of developing breast cancer in their lifetime. Women's from Latina Hispanic Islander Asian and Pacific breast cancer rates fall in between two major groupings while American Indian and Alaska Native women are on the lowest risk of developing breast cancer. Overall white women are more risk of developing breast cancer than Black women. This risk increases at an older age between 60 and 84.While Black women have the highest breast cancer rates among women under age 40. Black women make up a higher percentage of triple-negative breast cancer cases.

- **Hormone therapy:** Some birth control methods use hormones, which might increase breast cancer risk. These may include Oral contraceptives, birth control shot, birth control implants, Intrauterine devices (IUDs), birth control skin patches, vaginal rings etc. In Postmenopausal woman use of combined hormonal therapy increases the risk of developing breast cancer. When combined hormone therapy prescribed to a woman increases likelihood breast cancer may be found at a more advanced stage.

- **Birth control**
  Birth control methods use hormones for contraception, which may increase risk of breast cancer.

- **Oral contraceptives:** Most research studies have revealed that women using oral contraceptives pills have a slightly higher risk of breast cancer than women who have never used them. Once these contraceptive pills are discontinuing risk of breast cancer seems to go back to normal within about 10 years.

- **Birth control shot:** An injectable form of progesterone e.g. Depo-Provera given once every 3 months for birth control. Some research studies have suggest that women currently using birth-control shots have greater breast cancer risk, but some other studies have suggest it safe contraceptive shot.

- **Birth control implants, intrauterine devices (IUDs), skin patches, vaginal rings:** All of above forms of birth control measures have also contain hormones, which suggest risk of breast cancer growth. Some research studies have shown a link between use of hormone-releasing IUDs and breast cancer risk, but few studies have looked at the use of birth control implants, patches, and rings and breast cancer risk.

- Approximately 80% of breast cancers express estrogen receptors, progesterone receptors, or both. Endocrine therapies are remains the major treatment for these hormone receptor–positive cancers cases, substantially reducing the relapse rate after presentation with early-stage cancer. This includes using HRT (hormone replacement therapy) during menopause for period of 5 years and taking certain types of contraceptive pills. The risk of breast cancer is increase in combination with hormone replacement therapy.

- Local hormone therapy use is not related with an increase in breast cancer recurrence among women who are receiving a hormone therapy.

- A study conducted in UK suggests that use of different hormone replacement preparations for longer duration have greater risk of developing breast cancer.

- In hormonal therapy 4 types of medicines have been proven to decrease the risk of developing hormone-receptor-positive breast cancer in women at high risk. These drugs are SERMs selective estrogen receptor modulators eg. Tamoxifen and Raloxifene and the Aromatase inhibitors e.g. Exemestane and Anastrozole and above these four medicines are used as prophylactic drugs.

- Tamoxifen has been proven many time to reduce the risk of first-time hormone-receptor-positive breast cancer in both postmenopausal and premenopausal women at high risk.
- Raloxifene has been shown to reduce the risk of first-time hormone-receptor-positive breast cancer in postmenopausal women.
- Exemestane has been shown to reduce the risk of first-time hormone-receptor-positive breast cancer in postmenopausal women at high risk.
- Anastrozole has been shown to reduce the risk of first-time, hormone-receptor-positive breast cancer in postmenopausal women at high risk.
- Hormonal therapy medicines do not reduce the risk of hormone-receptor-negative breast cancer.

Risk factors of breast cancer which requiring further Study

Oral Contraceptives:

Some research studies have proven that taking oral contraceptives pills a little increases a woman's risk of developing breast cancer, simultaneously other research studies have suggest no effect on risk. A recent research study analysis or comparison showed that women who took oral contraceptives hormonal pills for long duration or more than 12 years had a slightly greater risk of breast cancer than women who did not take oral contraceptives. Once women

discontinue taking oral contraceptives pills for 10 years, their risk appeared to return to the baseline or normal, average risk.

The exact effect of oral contraceptives or birth control pills on breast cancer risk is still question of research studies.

Environmental Pollutants:

Extensive research studies are examining aspects of the environment that might contribute to develop breast cancer. But many studies have proven that breast cancer is not all the time likely to inherited factors. A possible link between environmental pollutants, such as pesticides, and an increased risk of breast cancer are studied, but no clear link has been identified.

Hence, current research evidence that has been published suggests that environmental pollutants are probably not the main cause of developing breast cancer.

Smoking:

It is already known that smoking increases a individual's risk of coronary artery disease and respiratory cancer like lung cancer, but many evidences of research reveals that there is no association between smoking and an increased risk of breast cancer. However, researchers continue to study the potential impact of smoking on breast cancer risk and, in some woman, they are able to find a link of breast cancer.

A recent research study revealed that women cigarette smokers, both through active and passive smokers, were indeed at higher risk of developing breast cancer. Another research study evidences, proposed that the effect of cigarette smoking on breast cancer risk was related to the time and duration of exposure in its study population. A young women smoker is at highest risk due to prolonged time exposure.

Although researchers are unable to find out association between smoking and breast cancer risk clearly, but smoking is strongly condemned because of its known impact on a individual's risk of lung cancer and coronary artery disease.

High-Fat Diet:

Several research studies have conducted to establish relationship between a high-fat diet and a woman's risk of developing breast cancer. A balanced diet is always preventing from many disorders and builds immunity against infectious or foreign bodies. Researchers also are investigating risk of breast cancer and high fat diet, they are also trying to find out the association saturated versus unsaturated fat eaten affect the risk of breast cancer.

Thus far, while there is a clear link between a high-fat diet and an increased risk of heart disease, the association between diet and breast cancer risk is unclear. Nonetheless, it is important to manage dietary fat intake in order to maintain a healthy body weight.

Antiperspirants:

Researchers are not able to established relationship between use of antiperspirants and risk of breast cancer. No research study has proven that the use of antiperspirant increases the risk of breast cancer.

Underwire Bras:

Research suggests that there is no evidence or association between underwire bras and the development of breast cancer.

Abortion:

Many research studies have conducted to identify relationship between abortion and developing risk of breast cancer. Hormonal changes occurs during pregnancy, so Some researchers have proven that induced abortion may result in a slight increase risk of developing breast cancer but same time other studies have shown no effect on risk.

So hence, there is not sufficient evidences that suggest women who have history of abortions are at increased risk of developing breast cancer.

Breast implants: In present time there is no evidence of an association between breast implants and breast cancer but having silicone breast implants and resulting scar tissue make it harder to diagnose problems of breast on regular mammograms. A rare type of cancer called anaplastic large cell lymphoma or ALCL is associated with the breast implants. A research study suggests that women who have history of cosmetic breast implantation do not have an increased risk of breast cancer.

Benign Breast Biopsy:

All type of benign tumours related to breast whenever suspected for malignancy found to be benign or non cancerous in biopsies or pathological examination.

Tobacco:

As it’s already known that tobacco have many carcinogens and appears to increase the risk of breast cancer, with the greater the amount chewing tobacco and the earlier in life that smoking began, the higher the risk.

Tall adult height:
Research shows that tall women before and after menopause have a little higher risk of developing breast cancer. It is an assumption that energy intake and diet early in young life which affect adult height are the factors that increase the risk. Further investigation is required to prove this fact.

CONCLUSION:

In this chapter we have discussed about etiology of breast cancer and concluded that no sole cause of breast cancer or exact cause identified by researchers till now. In this section we find many risk factors such as controllable or non controllable and possible factors. Hence it's a multifactorial condition.

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