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Review Article

# BREAST CANCER RISK FACTORS: PREVENTABLE AND NON-PREVENTABLE

R. Lakshmi*, Raju Athira, Joy Teena Mary, S. Vijayalakshmi

Department of Pharmacy Practice, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham University, Kochi, Kerala, India

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*E-mail: lakshmir87@gmail.com

**ABSTRACT**

Worldwide, breast cancer comprises 22.9% of all cancers (excluding non-melanoma skin cancers) in women. The incidence of breast cancer is rising in every country of the world especially in developing countries such as India. In 1940, the lifetime risk of a woman developing breast cancer was 5%, or one in 20. The American Cancer Society estimates that risk being 13% in 2012, or more than one in 8. Studies have shown that certain factors, called risk factors, increase the likelihood that a woman will develop breast cancer. Many of these risk factors are not reversible, but some can be modified. A "risk factor" is anything that increases the risk of developing breast cancer. Many of the most important risk factors for breast cancer are beyond control (non-preventable), such as age, family history, and medical history. However, there are some risk factors that are preventable, such as weight, physical activity, and alcohol consumption.

**KEY WORDS:** breast cancer, risk factors of breast cancer, incidence of breast cancer

## INTRODUCTION

Worldwide, breast cancer comprises 22.9% of all cancers (excluding non-melanoma skin cancers) in women. In 2008, breast cancer caused 458,503 deaths worldwide (13.7% of cancer deaths in women). Breast cancer is more than 100 times more common in women than in men, although men tend to have poorer outcomes due to delays in diagnosis.

The incidence of breast cancer is rising in every country of the world especially in developing countries such as India. In 1940, the lifetime risk of a woman developing breast cancer was 5%, or one in 20. The American Cancer Society estimates that risk being 13% in 2012, or more than one in 8. In many cases, it's not known why a woman gets breast cancer. In fact, 75% of all women with breast cancer have no known risk factors. However, not all women have the same risk of developing breast cancer during their lifetime. Studies have shown that certain factors, called risk factors, increase the likelihood that a woman will develop breast cancer. Many of these risk factors are not reversible, but some can be modified.

The presence of breast cancer risk factors does not mean that cancer is inevitable: many women with risk factors never develop breast cancer. Instead, risk factors help to identify women who may benefit most from screening or other preventive measures. Individual women should work with their clinicians to determine their own personal risk of breast cancer, based upon their own circumstances. It is important to remember that breast cancer can also occur in women who have no identifiable risk factors. The average woman has about a 10 to 15 percent chance of developing breast cancer if she lives into her 90s.

A "risk factor" is anything that increases the risk of developing breast cancer. Many of the most important risk factors for breast cancer are beyond control (non-preventable), such as age, family history, and medical history. However, there are some risk factors that can control (preventable), such as weight, physical activity, and alcohol consumption (Figure 1).

Epidemiological research informs the patterns of breast cancer incidence across certain populations, but not in a given individual. Approximately 5% of new breast cancers are attributable to hereditary syndromes and well-established risk factors accounted for approximately 30% of cases. [1, 2]

### Preventable Risk Factors

**Overweight:** Being overweight (especially in the waist) defined as having a BMI (body mass index) over 25 is associated with increased risk of breast cancer, especially for women after menopause. Fat tissue is the body's main source of estrogen after menopause, when the ovaries stop producing the hormone. Having more fat tissue means having higher estrogen levels, which can increase breast cancer risk. Being overweight also can increase the risk of the breast cancer coming back (recurrence) in women who have had the disease. Furthermore, studies have shown that obese women are more likely to have large tumors, greater lymph node involvement, and poorer breast cancer prognosis with 30% higher risk of mortality. Still, the link between extra weight and breast cancer is complicated and affected by other factors. For example, the location of the extra weight matters. Extra fat around your belly may increase risk more than the same amount of extra fat around the thighs or hips. [3]

**Lack of Exercise:** Research shows that exercise can reduce breast cancer risk. The American Cancer Society recommends engaging in 45-60 minutes of physical exercise 5 or more days a week. Exercise consumes and controls blood sugar and limits blood levels of insulin growth factor, a hormone that can affect how breast cells grow and behave. People who exercise regularly tend to be healthier and are more likely to maintain a healthy weight and have little or no excess fat compared to people who don't exercise. Fat cells make estrogen and extra fat cells make extra estrogen. When breast cells are exposed to extra estrogen over time, the risk of developing breast cancer is higher. [4]

**Diet:** Diet is a suspected risk factor for many types of cancer, including breast cancer. It's a good to restrict sources of red meat and other animal fats (including dairy fat in cheese, milk, and ice cream), because they may contain hormones, other growth factors, antibiotics, and pesticides. Eating too much cholesterol and other fats are risk factors for cancer, and studies show that eating a lot of red and/or processed meats is associated with a higher risk of breast cancer. A low-fat diet rich in fruits and vegetables is generally recommended. One recent study suggests that low-fat diets

may significantly decrease the risk of breast cancer as well as the recurrence of breast cancer. [5]

**Alcohol Consumption:** Studies have shown that breast cancer risk increases with the amount of alcohol a woman drinks. The primary mechanism through which alcohol causes breast cancer is increased estrogen levels. Alcohol can limit the ability to control blood levels of the hormone estrogen, which in turn can increase risk. Alcohol also may increase breast cancer risk by damaging DNA in cells. Compared to women who don't drink at all, women who have three alcoholic drinks per week have a 15% higher risk of breast cancer. It is estimated that the risk of breast cancer goes up another 10% for each additional drink women regularly have each day.A study of more than one million middle-aged British women concluded that each daily alcoholic beverage increases the incidence of breast cancer by 11 cases per 1000 women. [6]

**Smoking:** Smoking is associated with an increase in breast cancer risk. Smoking causes a number of diseases and is linked to a higher risk of breast cancer in younger, premenopausal women. Research also has shown that there may be link between very heavy second-hand smoke exposure and breast cancer risk in postmenopausal women. Breathing secondhand smoke increases breast cancer risk by 70% in younger, primarily pre-menopausal women. There is some evidence that exposure to tobacco smoke is most problematic between puberty and first childbirth. The reason that breast tissue appears most sensitive to chemical carcinogens in this phase is that breast cells are not fully differentiated until lactation. [7]

Smoking also can increase complications from breast cancer treatment, including:

- Damage to the lungs from radiation therapy
- Difficulty healing after surgery and breast reconstruction
- Higher risk of blood clots when taking hormonal therapy medicines.

**Hormone Replacement Therapy:** Current or recent past users of hormonal replacement therapy (HRT) have a higher risk of being diagnosed with breast cancer. Data exist from both observational and randomized clinical trials regarding the association between menopausal hormone replacement therapy (menopausal HRT) and breast cancer. The largest meta-analysis (1997) of data from 51 observational studies indicated a relative risk of breast cancer of 1.35 for women who had used HRT for 5 or more years after menopause. HRT-related breast cancers had adverse prognostic characteristics (more advanced stages and larger tumors) compared with cancers occurring in the placebo group, and HRT was also associated with a substantial increase in abnormal mammograms. Short-term use of hormones for treatment of menopausal symptoms appears to confer little or no breast cancer risk. [8]

There are two main types of HRT and each type of HRT seems to have a different effect on breast cancer risk.

- Combination HRT contains the hormones estrogen and progesterone
- Estrogen-only HRT contains only estrogen

Combination HRT increases breast cancer risk by about 75%, even when used for only a short time. Combination HRT also increases the likelihood that the cancer may be found at a more advanced stage, as well as increasing the risk that a woman diagnosed with breast cancer will die from the disease. Breast cancer risk increases the most during the first 2 to 3 years of taking combination HRT. Higher-dose combination HRT increases breast cancer risk more than lower-dose combination HRT. Breast cancer risk goes back down to average about 2 years after you stop taking combination HRT.

Estrogen-only HRT increases the risk of breast cancer, but only when used for more than 10 years. Estrogen-only HRT also can increase the risk of ovarian cancer. [9]

**Recent Oral Contraceptive Use:** Using oral contraceptives (birth control pills) appears to slightly increase a woman's risk for breast cancer, but only for a limited period of time. Women who stopped using oral contraceptives more than 10 years ago do not appear to have any increased breast cancer risk. Some studies have suggested that women who began using hormonal contraceptives before the age of 20 or before their first full-term pregnancy are at increased risk for breast cancer. The relative risk of breast cancer diagnosis associated with current and recent use of hormonal contraceptives did not appear to vary with family history of breast cancer. [10]

**Environmental Factors:** The main mechanisms by which environmental compounds increase breast cancer risk are acting like hormones, especially estrogen, or affecting susceptibility to carcinogenesis.[11] The evidence generally supports an association between breast cancer and polycyclic aromatic hydrocarbons (PAHs) and polychlorinated biphenyls (PCBs) dioxins and organic solvents. On the other hand evidence is still based on a relatively small number of studies.

**Non-Preventable Risk Factors**

**Age:** The risk of getting breast cancer increases with age. That's because the longer one live, there are more opportunities for genetic damage (mutations) in the body. And as one age, their bodies are less capable of repairing genetic damage. A woman is more than 100 times more likely to develop breast cancer in her 60s than in her 20s. according to the American Cancer Society, about 1 out of 8 invasive breast cancers develop in women younger than 45. About 2 out of 3 invasive breast cancers are found in women 55 or older. (Figure 2).If all women lived to age 95, about one in eight would be diagnosed with breast cancer at some point during their lives. However, the actual lifetime risk is lower than that, because 90% of women die before age 95, most commonly from heart attacks, strokes, or other forms of cancer. The probability of breast cancer rises with age, but breast cancer tends to be more aggressive in younger people.[12]

**Sex:** Being a woman is the most significant risk factor for developing breast cancer. Although men can get breast cancer, too, women's breast cells are constantly changing and growing, mainly due to the activity of the female hormones estrogen and progesterone. This activity puts them at much greater risk for breast cancer.Men have a much lower risk of developing breast cancer than women. In developed countries, about 99% of breast cancer cases are diagnosed in women; in a few African countries, which represent the highest incidence of male breast cancer, men account for 5–15% of breast cancer cases. The rate of breast cancer in men appears to be rising somewhat. Men diagnosed with breast cancer tend to be older than women with breast cancer. They are more likely to be diagnosed with hormone-receptor positive tumors, with about six out of seven cases being estrogen-receptor positive. The overall prognosis is worse for men than for women. [13]

**Menstrual History:** Women who started menstruating younger than age 12 have a higher risk of breast cancer later in life. The same is true for women who go through

menopause when they're older than 55. Over the past 15 years, girls have been starting puberty at younger ages. Breast development has started even earlier than menstrual periods. This unexpected shift has been attributed to the obesity epidemic and broad exposure to hormone disruptors, since a rise in hormones triggers the onset of breast development and puberty. The age when women go through menopause, however, has stayed about the same. The earlier the breasts form, the sooner they're ready to interact with hormones inside and outside the body, as well as with chemicals in products that are hormone disruptors. This longer interaction with hormones and hormone disruptors can increase risk. Also, when girls start menstruating at a younger age, the time between breast development and a first full-term pregnancy is usually longer than when menstruation happens later. During this time, breast tissue tends to be immature, overactive, and particularly sensitive to hormonal influences. The longer a woman menstruates, the higher her lifetime exposure to the hormones estrogen and progesterone. All of these factors are associated with a higher risk of breast cancer later in life. [14]

**Pregnancy History:** Lower age of first childbirth, compared to the average age of 24, having more children (about 7% lowered risk per child) have been correlated to lowered breast cancer risk in large studies. Women who haven't had a full-term pregnancy or have their first child after age 30 have a higher risk of breast cancer compared to women who gave birth before age 30. When breast cells are made in adolescence, they are immature and very active until the first full-term pregnancy. The immature breast cells respond to the hormone estrogen as well as hormone-disrupting chemicals in products. The first full-term pregnancy makes the breast cells fully mature and grow in a more regular way. This is the main reason why pregnancy helps protect against breast cancer. Pregnancy and breastfeeding reduce the overall number of menstrual cycles in a woman's lifetime, and this appears to reduce future breast cancer risk. [15] Women who give birth and breast-feed by the age of 20 may have even greater protection. In contrast, for instance, having the first live birth after age 30 doubles the risk compared to having first live birth at age less than 25. Never having children triples the risk. [16, 17]

**Breastfeeding History:** For women who do have children, breastfeeding may slightly lower their breast cancer risk, especially if they continue breastfeeding for 1 1/2 to 2 years. There is less benefit for women who breastfeed for less than a year. There are several reasons why breastfeeding protects breast health:

- Making milk 24/7 limits breast cells' ability to misbehave
- Most women have fewer menstrual cycles when they're breastfeeding resulting in lower estrogen levels
- Many women tend to eat more nutritious foods and follow healthier lifestyles (limit smoking and alcohol use) while breastfeeding.

Women who give birth and breast-feed by the age of 20 may have even greater protection. [18]

**Family History:** In 5% of breast cancer cases, there is a strong inherited familial risk. [19] Women with close relatives who've been diagnosed with breast cancer have a higher risk of developing the disease. If one have had one first-degree female relative (sister, mother, daughter) diagnosed with breast cancer, their risk is doubled. If two first-degree relatives have been diagnosed, their risk is 5 times higher than average. If one's brother or father has been diagnosed with breast cancer, the risk is higher. (Figure 4)

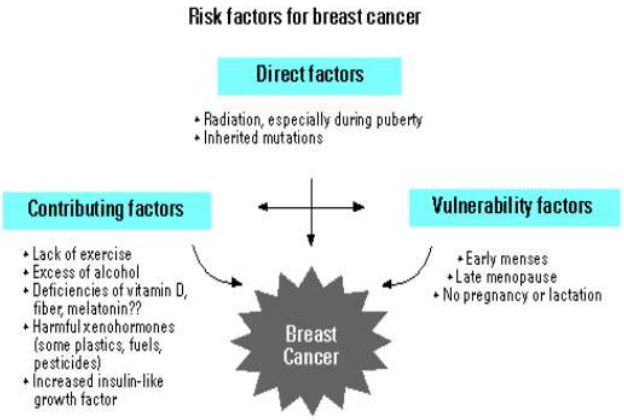



**Figure 1: Risk factors of breast cancer**

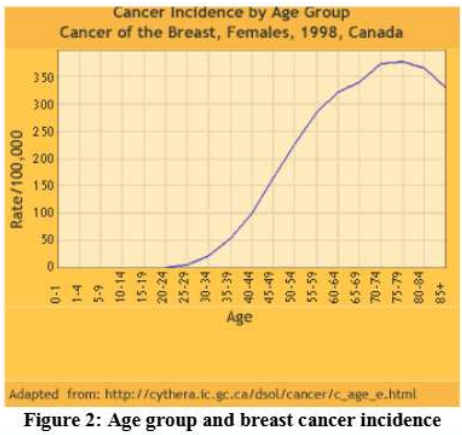



**Figure 2: Age group and breast cancer incidence**

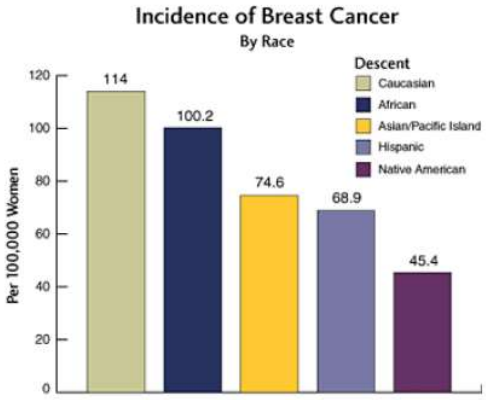



**Figure 3: Race and breast cancer incidence**

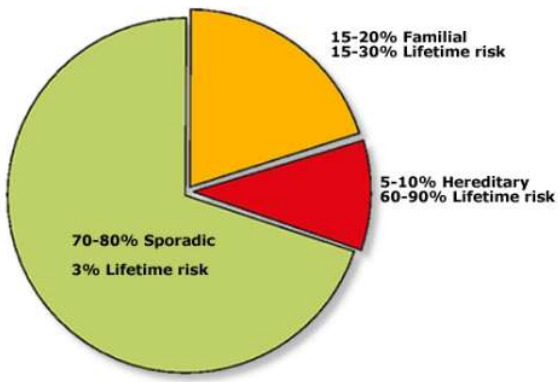



**Figure 4: Heredity and breast cancer incidence**

Two autosomal dominant genes, BRCA1 and BRCA2, account for most of the cases of familial breast cancer. Women who carry a harmful BRCA mutation have a 60% to 80% risk of developing breast cancer in their lifetimes. Other associated malignancies include ovarian cancer and pancreatic cancer. If a mother or a sister was diagnosed breast cancer, the risk of a hereditary BRCA1 or BRCA2 gene mutation is about 2-fold higher than those women without a familial history. Commercial testing for BRCA1 and BRCA2 gene mutations has been available in most developed countries since at least 2004. [20]

Hereditary non-BRCA1 and non-BRCA2 breast tumors (and even some sporadic carcinomas) are believed to result from the expression of weakly penetrant but highly prevalent mutations in various genes. For instance, polymorphism has been identified in genes associated to the metabolism of estrogens and/or carcinogens (CYP1A1, CYP1B1, CYP17, CYP19, COMT, NAT2, GSTM1, GSTP1, GSTT ), to estrogen, androgen and vitamin D action (ESR1, AR, VDR), to co-activation of gene transcription (AIB1), to DNA damage response pathways (CHEK2, HRAS1, XRCC1, XRCC3, XRCC5). Sequence variants of these genes that are relatively common in the population may be associated with a small to moderate increased relative risk for breast cancer. RAB11FIP1, TP53, PTEN and rs4973768 are also associated with increased risk of breast cancer. Rs 6504950 is associated with lower risk of breast cancer. Mutations in RAD51C confer an increased risk for breast and ovarian cancer. [21]

**Personal History:** People who have previously been diagnosed with breast, ovarian, uterine, or bowel cancer have a higher risk of developing breast cancer in the future. Mothers of children with soft-tissue sarcoma may have an increased risk of breast cancer. Men with prostate cancer may have an elevated risk of breast cancer, although the absolute risk remains low. If one have been diagnosed with breast cancer, they are 3 to 4 times more likely to develop a new cancer in the other breast or a different part of the same breast. This risk is different from the risk of the original cancer coming back (called risk of recurrence). [22]

**Radiation to Chest or Face before Age 30:** Women treated for childhood cancer with radiation therapy to the chest area have a much higher-than-average risk of breast cancer later in life. This risk is about the same as it is for women who have an abnormal breast cancer gene Breast cancer risk by age 50 was projected to be 10% for women who received lower-dose radiation therapy to the chest area to treat other childhood cancers. While lower than the risk faced by women who received high-dose Women who, as children or young adults, had radiation therapy to the chest area as treatment for another cancer (such as Hodgkin disease or non-Hodgkin lymphoma) have a significantly increased risk for breast cancer. This varies with the patient's age when they had radiation. If chemotherapy was also given, it may have stopped ovarian hormone production for some time, lowering the risk. The risk of developing breast cancer from chest radiation is highest if the radiation was given during adolescence, when the breasts were still developing. Radiation treatment after age 40 does not seem to increase breast cancer risk. Childhood radiation, this 10% risk is still higher than the average of 4% and identical to the projected risk by age 50 for first degree female relatives of someone with an abnormal BRCA2 gene. If one had radiation to the face as an adolescent to treat acne (something that's no longer done), they are at higher risk of developing breast cancer later in life. The amount of risk increase depends on how old they were when they had radiation. The increase in risk is highest if it was during adolescence. [23, 24]

**Race/Ethnicity:** White women are slightly more likely to develop breast cancer than African American. . Asian, Hispanic, and Native American women have a lower risk of developing and dying from breast cancer. Caucasian women are at a slightly higher risk of developing breast cancer than are African-American. (Figure3). The exception to this is African-American women, who are more likely to develop more aggressive, more advanced-stage breast cancer that than whites under the age of 40. African American women are also more likely to die from breast cancer. Some of these differences in outcomes may be due to less access to mammography and lower quality medical care, as well as various lifestyle patterns (eating habits, weight issues etc.) that are more common in some ethnic groups than in others. These factors can be changed and improved. Triple-negative breast cancer, which is more aggressive than other types, is more common in African American women. Triple-negative breast cancer is estrogen-receptor-negative, progesterone-receptor-negative, and HER2-negative. [25]

**Breast Cellular Changes / Breast Lesions:** Unusual changes in breast cells found during a breast biopsy (removal of suspicious tissue for examination under a microscope) can be a risk factor for developing breast cancer. These changes include overgrowth of cells (called hyperplasia) or abnormal (atypical) appearance. A previous breast biopsy result of atypical hyperplasia (lobular or ductal) or lobular carcinoma in situ increases a woman's breast cancer risk by four to five times. [26]

**Oophorectomy and Mastectomy:** Prophylactic oophorectomy (removal of ovaries) and mastectomy in individuals with high-risk mutations of BRCA1 or BRCA2 genes reduces the risk of developing breast cancer as well as reducing the risk of developing ovarian cancer. Because of a complex balance of benefits and risks of a prophylactic surgery it is recommended only in very specific cases. [27]

**DES Exposure:** Women who took a medication called diethylstilbestrol (DES), used to prevent miscarriage have a slightly increased risk of breast cancer. Women whose mothers took DES during pregnancy may have a higher risk of breast cancer as well. [28]

**Exposure to Estrogen:** The female hormone estrogen stimulates breast cell growth, exposure to estrogen over long periods of time, without any breaks, can increase the risk of breast cancer. Some of these risk factors are not under your control, such as:

- Starting menstruation (monthly periods) at a young age (before age 12)
- Going through menopause (end of monthly cycles) at a late age (after 55)
- Exposure to estrogens in the environment (such as hormones in meat or pesticides such as DDT, which produce estrogen-like substances when broken down by the body)

## CONCLUSION

The risk factors responsible for the causation of breast cancer may be population or region specific. Moreover, there are inherent factors that aid in the late presentation of breast cancer patients to a hospital. There is no sure way to prevent breast cancer. But there are things all women can do that might reduce their risk and help increase the odds that if cancer does occur, it is found at an early, more treatable

stage. It is important to identify these factors in order to bring down the incidence, morbidity and mortality due to this disease.

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