

# Modern interpretation of risk factors in breast cancer of women

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## ABSTRACT



Breast cancer is a major public health problem, being the most common cancer diagnosed in women and accounting for more than 1 in 10 new diagnoses of cancer each year. It is the most common neoplasm of women under the age of 40 and the second leading cause of cancer death in this age group, with more frequent detection of pathogenic mutations in breast cancer susceptibility genes. Women with BRCA<sub>1</sub> and BRCA<sub>2</sub> mutations are about 70% more likely to develop breast cancer. The incidence is rising in most countries and it is expected to have a growing trend in the next 20 years, despite the current efforts to prevent the disease. In order to improve the survival rate, it is necessary to make a diagnosis as early as possible and to initiate the appropriate therapeutic management as soon as possible. Therefore, in order to detect breast formations, mammography screening is very important, breast density being an important factor in predicting the risk of breast cancer. Thus, the presence of high breast density represents a 4-6 times higher risk of developing breast cancer compared to women with low breast density. Aging and menopause are also risk factors for breast cancer. Hormone replacement therapy for postmenopausal women has the benefit of relieving symptoms such as hot flashes, depression or sleep disturbances, but it increases the risk of developing breast cancer.

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## Introduction

Breast cancer is the most common type of cancer worldwide. At the end of 2020, breast cancer had an incidence of 47.8%, with a mortality rate of 13.6%. Prostate cancer was on the second position, with an incidence of 30.7% and a mortality rate of 7.7%. The following places were occupied by lung, colorectal and cervical cancer [1].

Breast cancer has become the most common cancer globally since 2021, accounting for 12% of all new annual cancer cases worldwide, according to the World Health Organization. It is the most commonly diagnosed cancer in women in the United States, in addition to skin cancers, and about one in 8 women (about 13%) will develop invasive breast cancer throughout their lifetime, compared to a man's lifetime risk of breast cancer, which is about 1 in 833 [2].

By 2022, it is estimated that about 30% of the newly diagnosed cancers in women will be breast cancer. In

women under the age of 45, breast cancer is more common among women of color than in white women, and consequently the death rate is higher for this group. For Asian, Hispanic, and Native American women, the risk of developing and implicitly the risk of dying from breast cancer is lower [3].

Most patients discover their disease during a routine screening, or by accidental discovery of a lump, a change in the shape or size of the breast or a nipple discharge. Also, the history of cosmetic augmentation surgery may be a source of concern about breast implant illness [3,4]. These, along with mastalgia, are relatively common, causing significant anxiety in the patient and leading to the appointment to a specialist. This will include an initial assessment and a detailed medical history along with physical examination. Mammography is usually preferred to support the diagnosis of breast cancer, but ultrasonography appears to be more sensitive in women under 30 years of age [5].

About 5-10% of breast cancers may be related to known and inherited genetic mutations, and breast cancer in the history of first-degree relatives may double the risk of developing the disease. However, fewer than 15% of women who develop breast cancer have a family member diagnosed with it, with the male hereditary collateral component present in 50% of the cases [6].

Mutations in the BRCA<sub>1</sub> and BRCA<sub>2</sub> genes should be diagnosed in cases where a hereditary predisposition is suspected. On average, women with a BRCA<sub>1</sub> mutation have a lifetime risk of up to 72% of developing breast cancer, and those with a BRCA<sub>2</sub> mutation have a 69% risk, and tend to develop more often with breast cancer. Some women have a higher risk of breast cancer due to a higher rate of BRCA mutations, as colorectal cancer does [7].

About 85% of breast cancers occur in women who do not have a family history of breast cancer. In these cases, they develop due to genetic mutations that occur as a result of aging and life in general, rather than inherited mutations [7,8].

The article is an analysis of several studies on the assessment of risk factors for breast cancer. The most common factors and their influence on patient groups were discussed: young or menopausal women, the presence of genetic mutations, patients undergoing hormone replacement therapy, women with a healthy or unfavorable lifestyle who associate or do not consume alcohol and tobacco. The studies were accessed through several scientific platforms, such as PubMed, Scopus, etc.

## Discussion

Breast cancer is a heterogeneous disease, whose complexity is genetically rooted and reflected in its phenotypic characteristics [6,8].

Luminal cancers (A and B) are characterized by the expression of estrogen receptors (ER) and/or progesterone receptors (PgR), while tumors enriched with human epidermal growth factor 2 (HER<sub>2</sub>) show the overexpression of HER<sub>2</sub> and/ or inherent gene amplification. In triple-negative breast cancer (TN), none of the above targets are identifiable or adequately represented for therapeutic use [7-9].

The risk of developing breast cancer in postmenopausal women is associated with changes in circulating sex hormone levels and the administration of hormone replacement therapy (MHT). Such therapy is used to relieve common menopausal symptoms such as hot flashes, sleep disturbances, depression, and muscle or joint pain [10,11].

The initiation of hormone therapy for menopause may be a safe option for women under the age of 60 who have entered menopause less than 10 years before, who have no history of breast cancer and who are not associated with diseases such as stroke, thromboembolic disorders, active liver disease or coronary heart disease [12,13].

Elevated levels of endogenous estrogen are associated with an increased risk of breast cancer (especially the hormone-positive form of disease) for both pre- or postmenopausal women. However, the association of estrogen levels with the risk of breast cancer among premenopausal women can be difficult to measure due to changes in the menstrual cycle [14,15].

A multicenter study on 767 premenopausal women with breast cancer and 1,699 control patients measured estradiol, estrone, androstenedione, dehydroepiandrosterone and testosterone and associated positive for breast cancer [13].

At the same time, hormone therapy combined with estrogen/ progesterone in postmenopausal women with the uterus present increases the risk of subsequent positive ER breast cancer. In women with a history of hysterectomy, replacement with a single estrogen has not been associated with an increased risk of breast cancer [11,14].

A study by Ellingjord et al. analyzed hormonal risk factors, including reproductive factors (age at first birth, number of pregnancies, breastfeeding), as well as other hormonal factors (the use of oral contraceptives, intrauterine devices and menopausal hormone replacement therapy). The latter included only the use of estrogen or the use of combination therapy with estrogen and progestin. The analysis showed that the body mass index, the age at first birth, the age at menopause, the duration of use of oral contraceptives or intrauterine devices, and the use of hormone therapy at menopause were positively associated with the risk of breast cancer. The age of onset of menarche and the number of pregnancies were associated with a low risk [16].

Compared to women who have never been pregnant, those with more than 3 pregnancies have a risk of about 40% or less of developing luminal breast cancer. For HER<sub>2</sub>-positive and triple-negative tumors, there were no statistically significant associations. The heterogeneity test comparing triple negative cancer with luminal type A cancer was statistically significant. Older age at first birth has been associated with an increased risk of breast cancer in general. Mothers older than 30 years at first birth had a slightly increased risk of developing A-like luminal tumors and HER<sub>2</sub>-negative B-like luminal breast cancer. The heterogeneity test comparing each subtype with A-like luminal breast cancer was not statistically significant for age at first birth [16].

Abubakar et al. conducted an analysis of two study populations from Poland and the United Kingdom. The analysis included 2,498 women with similar luminal-like tumors, ER + and/ or PR + for which complete data on scores based on image analysis for ER, PR, HER<sub>2</sub> and Ki67 could be accessed. Patients were screened at the Eastern Cancer Registry and Information Center. The study included women under the age of 55 diagnosed with invasive breast cancer from 1991-1996. The data on the relevant clinical-pathological features, including ER, PR,

HER2, histological grade, tumor size, lymph node involvement, endocrine therapy and systemic therapy were obtained from the clinical records. Among the patients included in this analysis, there were 316 deaths due to breast cancer. The results showed in both populations of the study that most tumors (82%) were of medium or low histological grade and only 18% of high grade, and approximately 97% of the detected tumors were classified as stage I and II disease. Small (<2 cm) and intermediate (2–5 cm) tumors were predominant in both studies (98% and 97% for the Polish population, respectively). About 70% of the tumors were invasive ductal carcinomas. Only 9% of the patients had HER2 + and this did not differ on the study population [17].

A recent meta-analysis found a positive association between high blood pressure and the risk of breast cancer [18,19]. This was recently confirmed by a cohort study that reported a positive association between arterial hypertension and breast cancer mortality, supporting it as an independent risk factor for breast cancer [20].

Smoking has potential breast carcinogens, and it has been recently shown to be an increased risk factor for ER-positive breast cancer [21].

Breast cancer is the most commonly diagnosed cancer in women worldwide, and mammographic breast density (MD) assessment is one of the strongest factors for assessing the risk of developing this disease. Women with high breast density have a 4-6 times higher risk of developing breast cancer compared to women with low breast density [22-25]. However, studies analyzing the relationship between MD and endogenous plasma hormones have shown insufficient results [26-30]. MD may be an inherited trait or influenced by breast cancer risk factors [31,32].

A study by Howell et al. reviewed several available mammographic density data in relation with breast cancer risk [33]. An overview of 42 studies of white breast density (dense breast tissue appears white on mammography, while adipose tissue is radiolucent and it appears black) visually assessed on mammography indicated that the relative risk of breast cancer for women with a density of 70% or more was 4.64 times higher compared to women with less than 5% density.

In this report, the magnitude of the risk was higher using percentage density than for other visual density estimation methods, such as Wolfe patterns or the Breast Imaging Reporting and Data Classification (BI-RADS), which divides density into four categories, visually evaluated and widely used in the US [34].

Randomized clinical trials have shown that both MHT with estrogen alone and estrogen plus progestogen increase MD in postmenopausal women [35-38]. The Women's Health Initiative (WHI) study found that postmenopausal women who received combined estrogen plus progesterone

significantly increased the incidence of breast cancer over a 5-year period compared to the placebo group. In addition, they showed that the frequency of mammograms with suspicious findings in the estrogen plus progesterone group was higher than in the placebo group [39].

The presence of estrogen receptors in the structure of benign breast formations offers the opportunity to use tamoxifen (a selective modulator of estrogen receptors) to treat this pathology. Some authors suggest that low doses of the drug may be effective in treating benign proliferative lesions with a low incidence of side effects and a potential benefit in preventing the development of premalignant lesions [40].

The change in MD over time is not influenced by the typical risk factors for breast cancer. The factors most strongly associated with MD change are age, body mass index, pregnancy and physical activity [41-46].

A high BMI has been positively associated with postmenopausal breast cancer [47,48]. Several studies have reported an inverse relationship between being overweight and the risk of developing breast cancer at premenopause [49]. An increased body mass index is often associated with lifestyle. Thus, the most consistent dietary risk factor for breast cancer is alcohol, and alcohol consumption has been associated with higher estradiol levels and increased mammographic density in women with breast cancer and control [50,51].

In a large prospective study that included mainly postmenopausal women with a healthy lifestyle, the risk of breast cancer was low, especially for ER-positive breast tumors [52,53]. The Nurse's Health Study cohort found a decrease in the risk of menopausal breast cancer, especially ER-positive, among women who did not use MHT and adopted a healthy, alcohol-free lifestyle and without any weight gain [54].

The UK Biobank study found that a healthy lifestyle including diet, regular physical activity, smoking cessation and alcohol consumption mitigates the impact of genetic factors on breast cancer [55].

An important aspect that is difficult to assess is mental health, as it is known that depression affects the immune status and immune deficiencies can facilitate the appearance and progression of tumors. Many studies suggest an influence of psychological factors on survival, but this link could be influenced by other factors (stage, prognosis, aggressiveness of treatment, adherence to treatment) [56-59].

An analysis of BRCA<sub>1</sub> and/or BRCA<sub>2</sub> mutations associated a later onset of breast cancer in women who had a healthy lifestyle [60,61]. An unfavorable lifestyle can accelerate aging, and aging increases the risk of breast cancer.

According to the Surveillance, Epidemiology, and End Results (SEER) database, the likelihood of a woman

developing breast cancer in the United States between 2013 and 2015 by age range was [61]:

- 0 - 49 years - 2.1% (1 in 49 women)
- 50 - 59 years - 2.4% (1 in 42 women)
- 60 - 69 years - 3.5% (1 in 28 women)
- 70 years and over - 7.0% (1 in 14 women)
- lifetime - 12.9% (1 in 8 women)

Numerous studies have evaluated the incidence of breast cancer in women by age and ethnicity. A study conducted in the United States showed a higher frequency of breast cancer among white women [61]. Many of the racial differences are associated with the presence of risk factors and lifestyle. A cohort study of 156,000 postmenopausal women showed that the age-related incidence of breast cancer for white women was higher than for other groups. The presence of risk factors for breast cancer explained the differences for all groups except African Americans [62].

Mutations in the BRCA<sub>1</sub>/ BRCA<sub>2</sub> genes affect only a small number of women, while variation in the location or susceptibility of low-impact common single-nucleotide polymorphisms (SNPs) may be responsible for the increased incidence. Common places with low penetration have recently been identified. Their polygenic inheritance is associated with an increased risk of breast cancer [63,64]. SNPs are common changes in the DNA code that are thought to be non-functional variants that occur frequently outside of functional genes. However, the number of validated SNPs associated with the risk of breast cancer has now exceeded 70 and it is believed that there may be as many as hundreds that influence the risk of breast cancer [65,66].

Research has shown that DNA methylation is influenced by aging. Telomere length has been proposed as a biomarker of biological age and as a risk factor for cancer. Some studies have shown conflicting results between the association of telomere length and the risk of breast cancer. A healthy lifestyle can reduce the rate of telomere shortening and delay the onset of age-related diseases, including breast cancer [67-70].

## Conclusions

This paper highlights the complexity of risk factors and their mechanisms of action in relation to the incidence of breast cancer. The risk factors for breast cancer are many, the most incriminated being genetic predisposition, the administration of hormone replacement therapy, age and lifestyle.

High levels of endogenous estrogen increase the risk of breast cancer (especially hormone-positive breast cancer) in both postmenopausal and in premenopause women. Hormone therapy for menopause can be a safe option for women under the age of 60, with no history of breast cancer and who have been menopausal for up to 10 years.

Combination hormone therapy at menopause for women with intact uterus increases the risk of ER-positive breast cancer. The level of endogenous hormones has been associated with an increase in the mammographic density of the breasts. Periodic mammographic screening is an alternative to the early detection of potentially malignant breast lesions.

High body mass index has also been positively associated with postmenopausal breast cancer. Alcohol intake is associated with increased mammographic density, and smoking with increased risk of ER-positive breast cancer.

The most common cause of breast cancer among young women is the presence of BRCA<sub>1</sub> or BRCA<sub>2</sub> mutations. Patients with these mutations are about 70% more likely to develop breast cancer. Of the total number of cases diagnosed with breast cancer annually, only 5-10% of the tumors are associated with the presence of genetic mutations.

## Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

## Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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