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The Etiology of Breast Cancer

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Abstract: The etiology of breast cancer is attributed to a complex interaction between various modifiable and non-modifiable factors. This etiology is determined by genetics, environmental, nutritional, hormonal, and heritable elements that contribute to the development of this disease. Risk factors include prior history of breast cancer, positive family history, obesity, tall stature, smoking, alcohol consumption, early menarche, late menopause, sedentary lifestyle, nulliparity and hormone replacement therapy. Factors associated with decreased risk of breast cancer include multiparity, history of breastfeeding, physical activity, weight loss, and prophylactic surgical and medical interventions. In the United States, approximately one in eight women will be diagnosed with breast cancer in her lifetime. This disease is more common in white, post-menopausal females. Risk increases with older age with about 80% of breast cancer patients being older than 50 years. Analyzing the etiology of breast cancer allows for the development of improved screening and treatment interventions. In this chapter, the etiology of breast cancer along with the risk factors associated with this disease are discussed.

Keywords: breast cancer risk factors; ethnicity and breast cancer; etiology of breast cancer; family history of breast cancer; genetics of breast cancer

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INTRODUCTION

In the United States, there is a 12.3% average life risk that a woman will be diagnosed with breast cancer in her lifetime (1). This makes this disease the second most common cancer for women in the United States following skin cancer. The etiology of breast cancer is a complex interplay between multiple risk factors including prior history of breast cancer, positive family history, obesity, tall stature, smoking, alcohol consumption, early menarche, late menopause, sedentary lifestyle, nulliparity and hormone replacement therapy. Factors associated with decreased risk of breast cancer include multiparity, history of breastfeeding, physical activity, and weight loss. The influence of factors such as obesity and fertility on the etiology of breast cancer is displayed by the continued increase of breast cancer incidence rates of about 0.5% annually which has been attributed to a national increase in body weight and a decrease in fertility (1). Breast cancer is much more likely to occur in females than males, and it is also highly associated with advancing age and race with White females having the highest overall rates of breast cancer followed by Black, Asian, and Hispanic females respectively. Women with a first-degree relative who have had breast cancer are twice to three times more likely to develop breast cancer in their lifetime (2). The goal of this chapter is to explore the etiology of breast cancer to help provide a better understanding of the risk factors of this disease to potentially aid further research into the prevention and management of this disease.

FACTORS AFFECTING BREAST CANCER RISK

As noted, there are multiple interactive factors that impact breast cancer occurrences and in the subsequent sections the main features of these will be discussed.

Gender

Annually about 280,000 women and 3,000 men are diagnosed with breast cancer in the United States. Women are therefore about 100 times more likely to develop breast cancer compared to men (3). The more pronounced prevalence of breast cancer in women is mainly due to higher estrogen and progesterone stimulation. In post-menopausal women, the amount of circulating estrogens and androgens has been shown to be positively correlated with the risk of breast cancer (4). In men, the increase in estrogen to androgen ratio that is either due to estrogen excess or androgen deficiency is positively correlated with the risk of breast cancer (5). Also, both pre-menopausal and post-menopausal women experience more alternations of sex hormone levels in their lifetime compared to men resulting in higher breast cancer risk (6).

Age

Most cases of breast cancer are diagnosed in women older than 50 years, and the breast cancer risk continues to increase with advancing age (7–9). The Surveillance,

Epidemiology, and End Results (SEER) database showed that the probability of a woman developing breast cancer is 2.4% in ages 50 to 59, 3.5% in ages 60 to 69, and 7.0% in ages 70 and older (10). The increased breast cancer incidence with advancing age parallels the age dependence of many common cancers that is partly due to age-related increase in carcinogenesis and the accumulation of cellular modifications throughout time (11). There is also a relationship between age of diagnosis and outcome prognosis. Women diagnosed with breast cancer at an age lower than 50 have lower survival rates than those diagnosed at ages between 50 and 70 (9). The lower survival rate in younger patients is most likely due to the greater occurrence of highly aggressive triple negative breast cancer in patients 40 years old or younger.

Heritable factors and cancer genetics

Personal history of breast cancer is associated with increased, but still low, risk of developing breast cancer in the contralateral breast. The average risk of breast cancer survivors developing breast cancer on the opposite breast is estimated to increase by 0.5% each year following their initial cancer diagnosis (12). This increased risk could be largely attributed to increasing age since it is only slightly larger than the age-related increase in breast cancer in patients without prior history of breast cancer.

A first-degree family history of breast cancer increases the risk of breast cancer significantly. Studies show that the risk of breast cancer is doubled in a woman with a first-degree relative with prior breast cancer history. First-degree relatives for women are mother, sister, and daughter while second-degree relatives are grandmother, aunts, and nieces. A woman who has two first-degree relatives who have had breast cancer has triple the risk of a woman with no family history of breast cancer (13). According to a large cohort study of over 5,000,000 women, those who had a second-degree relative with breast cancer, but no first-degree relative with this history, had a 20% increased risk when the relative had carcinoma in situ and 30% when the cancer was invasive (14).

The significant association between positive family history and increased breast cancer risk is linked to having gene abnormalities. Most women who test positive for a gene associated with hereditary breast cancer have a pathogenic variant in either breast cancer susceptibility gene 1 (BRCA1) or breast cancer susceptibility gene 2 (BRCA2). According to a large prospective study, the cumulative cancer risk is 72% (95% CI 65 to 79 percent) in BRCA1 mutation carriers and 69% (95% CI 61 to 77 percent) in BRCA2 mutation carriers (15). Breast cancer incidence was also shown to increase in early adulthood until the average age of 35 years for BRCA1 carriers and until the average age of 45 years for BRCA2 carriers. The overall risk of breast cancer is about 3% higher in carriers of BRCA1 mutations compared to women with BRCA2 mutations (16–18).

Geography, ethnicity and race

Breast cancer incidence differs around the world. Incidence rates of breast cancer are higher in North America, North and West Europe, Australia, and New Zealand. However, the mortality rate of breast cancer is similar around the world (19).

In the United States, breast cancer risk differs among different race groups with the highest overall incidence of breast cancer being found in White women (131.8 per 100,000) followed by Black women (124.7 in 100,000) (20). The risk is decreased among Asian/Pacific Islander, Hispanic, American Indian/Alaskan Native women. It is important to note that although white women have the highest overall risk, black women have the highest risk of early onset breast cancer under the age of 45 years old (21) Black women also have higher breast cancer mortality rate and are more likely to present with advanced disease (22).

Obesity

Obesity is associated with an overall increased risk of breast cancer. The link between increased Body Mass Index (BMI) and breast cancer is found primarily in post-menopausal women that form estrogen positive breast cancer (6, 23). However, the relationship between obesity and risk of breast cancer differs based on menopausal status. According to data obtained from several studies, a higher BMI of ≥30 kg/m^2 has been shown to be associated with post-menopausal breast cancer risk (24–27). According to a meta-analysis of several studies, the relative risk of breast cancer among obese post-menopausal women is 1.1 per 5 BMI units (95% CI 1.1–1.2) (28). The higher estrogen levels among obese women have been attributed to this association. This reasoning is further strengthened by the fact that a higher body fat percentage among women with a normal BMI is also associated with a higher breast cancer risk (29). However, in premenopausal women, a higher BMI is reported to be associated with a reduced breast cancer risk (30). The cause of this inverse relationship is not yet known.

Stature

Tall stature has also been associated with increased risk of breast cancer (3, 31). According to data from seven prospective cohort studies that included more than 337,000 women, increased height is an independent risk factor for breast cancer. The relative risk of breast cancer for women 1.75 meter (about 69 inches) or taller compared with women shorter than 1.60 meter (about 63 inches) were 1.22 for all women with a relative risk of 1.42 for premenopausal women and 1.28 for postmenopausal women (32). There is no definitive conclusion on the reason for the association between height and breast cancer. However, there are proposed explanations of nutritional, genetic and environmental factors during early childhood that play an effect on growth hormone release having direct impact on future breast cancer development (32).

Physical activity and nutrition

Several studies have shown that there is an association between increased physical activity and lower risk of breast cancer (33–35). As an example, a large-scale meta-analysis of more than 230,000 breast cancer cases and millions of controls has shown that the risk of breast cancer is lower among women who exercise regularly compared with those who are least active (33). Physical activity is protective against the development of breast cancer in all women including those

with and without a family history of this disease (6). Both physical activity and dietary patterns are also linked with BMI which, as earlier discussed, if elevated to the level of obesity is strongly associated with the risk of developing breast cancer in post-menopausal women. Exercise has been linked to reduced estrogen and insulin levels which could also play an important factor in reducing breast cancer risk (36).

With regards to nutrition, a 20-year-long prospective study of post-menopausal women showed that a low-fat diet is associated with higher breast cancer survival rates (37). Overall, the consumption of red meats, processed foods, soy products, and fatty foods is linked to increased risk of breast cancer while increased consumption of fruits, vegetables, and fiber is linked to decreased risk (38). However, there are still several inconsistent findings with regards to the association and degree of impact these factors have on breast cancer development because different studies have yielded differing outcomes (38–40). Further research in the form of randomized trials and data gathering is needed to make a definite conclusion.

Alcohol consumption and smoking

A meta-analysis of more than 100 studies reported a positive association between breast cancer and low alcohol consumption (< 3–4 drinks/week), and high consumption (> 20 drinks/week), compared to no alcohol consumption (41). According to a large prospective study looking into the relationship between alcohol and breast cancer, there was a small increase in risk of breast cancer with 3 to 6 drinks/week compared with abstainers, with a relative risk of 1.15 (95% CI 1.06–1.24) (42). Lifetime alcohol intake was reported to be linearly correlated with breast cancer risk and risk was most strongly associated with very early and very late adult life drinking habits (43). The link between alcohol consumption and breast cancer risk may be related to alcohol's effect on estrogen metabolism causing an increase in blood estrogen levels. A cross-sectional study of the relationship between breast cancer risk and hormone concentration among post-menopausal women found that estrogen levels, that correlate with increased breast cancer risk, are increased in women who drink alcohol than in those who do not while dehydroepiandrosterone sulphate (DHEAS) and sex hormone-binding globulin (SHBG) levels were decreased (44).

Smoking has been shown by many studies to be associated with increased breast cancer risk. According to one meta-analysis of several prospective studies, the risk of breast cancer was higher among women with a history of smoking with a relative risk of 1.10 (95% CI 1.02–1.14) (45). In one prospective study of more than 100,000 women, smoking was associated with a 5% increase in the risk of breast cancer particularly in women who started smoking as an adolescent (46).

Menarche and menopause

Younger age at menarche and later age of menopause increases breast cancer risk (47). These investigators reported that relative risk for breast cancer, attributable to late onset menopause, increased by a factor of 1.029 (95% CI 1.025–1.032) for each added year of menopause onset. Breast cancer risk attributable to early

menarche is increased by a factor of 1.050 (95% CI 1.044–1.057) for every year younger at menarche (47). The younger the woman at menarche, the higher the risk of her developing breast cancer in the future. The effects of early menarche and late menopause on breast cancer has been attributed to greater lifetime exposure to endogenous estrogen. However, several studies have shown a more significant increase of breast cancer risk in women with early menarche compared to older age of menopause (47, 48). This suggests that the cause of this correlation is not entirely due to the duration a woman is exposed to high estrogen levels in her lifetime. Further research regarding the difference in breast cancer risk between early menarche and late menopause is needed to investigate the cause behind these findings.

Reproductive history and breastfeeding

Multiple studies have shown that both multiparity and breastfeeding have a protective effect against breast cancer. Breast feeding for at least six months has been shown to have the most effect in decreasing breast cancer risk. Data obtained from 47 epidemiological studies in 30 countries found that on average, women with breast cancer had less births and less or shorter breastfeeding history. The relative risk of breast cancer decreased by 4.3% (95% CI 2.9–5.8) for every one year of breastfeeding in addition to a decrease of 7.0% (95% CI 5.0–9.0) for each birth (49). There are also findings that this reduction in breast cancer was most significant in receptor negative breast cancers thus reducing aggressive disease subtypes (50).

Endogenous estrogen and hormonal therapy

Higher levels of estrogen in premenopausal and post-menopausal women have been associated with increased risk of breast cancer. A systematic review that analyzed data from several epidemiologic studies found that in six prospective studies, serum estradiol concentration of 329 women who developed breast cancer later in their life had higher estradiol blood concentrations compared to women who did not subsequently develop breast cancer (51). The reported estradiol concentration was 15% greater in those who developed breast cancer (CI 95% 6%–24%).

Post-menopausal women without a history of a total hysterectomy who underwent combined estrogen and progesterone replacement therapy have been shown to have increased risk of breast cancer (52). Multiple observational studies have reported an increased risk of breast cancer with use of menopausal hormone therapy, including unopposed estrogen therapy and combined estrogen-progestin therapy, for a prolonged duration (49, 53). The use of combined estrogen-progestin therapy for a short period of time, which was defined as four years or less, did not significantly increase breast cancer risk (54). However, both short-term and long-term use combined therapy has been linked to increased difficulty of breast cancer mammographic detection. The short-term use of unopposed estrogen therapy had similar outcomes to combined estrogen-progestin therapy neither of which caused increased risk (53). However, there was increased risk with long-term use of more than 10 years.

CONCLUSION

Breast cancer is caused by a complex interplay of multiple factors including age, genetics, environment, and reproductive history and probably yet unknown factors. The risk of breast cancer increases with older age and is most common in post-menopausal women. Genetics and heritable factors play an important role in the development of breast cancer. A first-degree family history of breast cancer significantly increases breast cancer risk. Potentially modifiable factors including obesity, alcohol consumption, smoking, physical inactivity, and replacement hormonal therapy have all been associated with increased breast cancer risk. Women's reproductive history also affects risk with nulliparity associated with increased rates compared to multiparity. Breast cancer is the leading cancer affecting women in the United States and globally. Being aware of its etiology aids understanding its pathophysiology and helps bring into focus important preventative measures that can be taken to reduce risk. Screening measures, treatment modalities, and patient counseling and education can all be enhanced by understanding the etiology of breast cancer.

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