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Non-Hereditary and Hereditary Risk Factors of Breast Cancer

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Abstract: Breast cancer is a worldwide health concern with the incidence rate increasing from year by year. Breast cancer is the most commonly diagnosed cancer among women and is the leading cause of cancer-related mortality among women in both developed and developing countries. Breast cancer initiation and progression is a complex, multistage process. Breast cancer is caused by inherited or acquired genetic changes in the somatic cells of the breast. In spite of significant advances in breast cancer research, there are still many unresolved concerns. Therefore, the investigation of risk factors associated with breast cancer continues to be a topic of interest and research. The main risk factors in the development of breast cancer may be unchangeable factors such as genetics, age and gender and may also be changeable factors such as those associated with lifestyle and environment. By recognizing breast cancer risk factors, it is possible to reduce the risk of developing this cancer and thus reduce the mortality associated with it, especially among women with these risk factors. This study aims to present the latest developments in the field of studying and identifying risk factors for breast cancer, as this topic is still one of the most important topics that are focused on reducing the risk of breast cancer and finding effective therapies to treat patients with this disease. To achieve this aim, we focused on the latest studies that have worked to identify risk factors for breast cancer. As a result, risk factors have been found to be either changeable or unchangeable. Changeable factors can be managed, while unchangeable factors are still being researched in order to find the most effective therapies to either prevent or control breast cancer.

Keywords: Breast cancer, Non-hereditary risk factors of breast cancer, Hereditary risk factors of breast cancer, Breast cancer genes

Introduction

Subdivide Cancer is a disease that occurs when a cell loses control of its normal growth and reproduction processes due to exposure to a factor that leads to a genetic mutation. Thereafter, the number of mutant cells increases and tumor forms as a result of cellular proliferation. Cancer cells have features that distinguish them from normal cells such as the ability to possess independent growth signals, lack of response to anti-growth signals, lack of response to apoptotic signals, and the ability to form new blood vessels, invade tissues, and metastasize (Açıkgoz & Akal -Yıldız, 2017). Breast cancer is caused by changes in the cells of the breast. Breast cancer often starts in the cells that line the milk ducts; therefore, this type is called ductal carcinoma. However, breast cancer may start in the lobules that house the milk-producing glands, therefore this type of cancer is called lobular carcinoma. Breast cancer receives the most attention compared to other cancers in women (Edward et al., 2021). According to World Health Organization (WHO) statistics in 2022, nearly 3 million new cases of breast cancer and 670,000 deaths were recorded globally. More than 99 % of these cases were among women (World Health Organization International Agency for Research on Cancer, 2024). In countries with a low human development index, 1 in 27 women are diagnosed and 1 in 48 women die due to breast cancer. This rate drops dramatically in countries with a high human development index, where one in 12 women will be diagnosed with breast cancer and one in 71 women will die (Momenimovahed & Salehiniya, 2019).

While there are many uncertainties surrounding the origin of breast cancer, there is evidence that the risk of developing breast cancer is related to many factors. Despite the variety of treatments available for breast cancer, the number of deaths associated with breast cancer remains high. For this reason, many specialized agencies are examining the risk factors associated with breast cancer in order to take action to reduce the incidence of breast cancer. Any substance, disease, or characteristic of an individual that increases the likelihood of developing breast cancer is a risk factor (Kashyap et al., 2022).

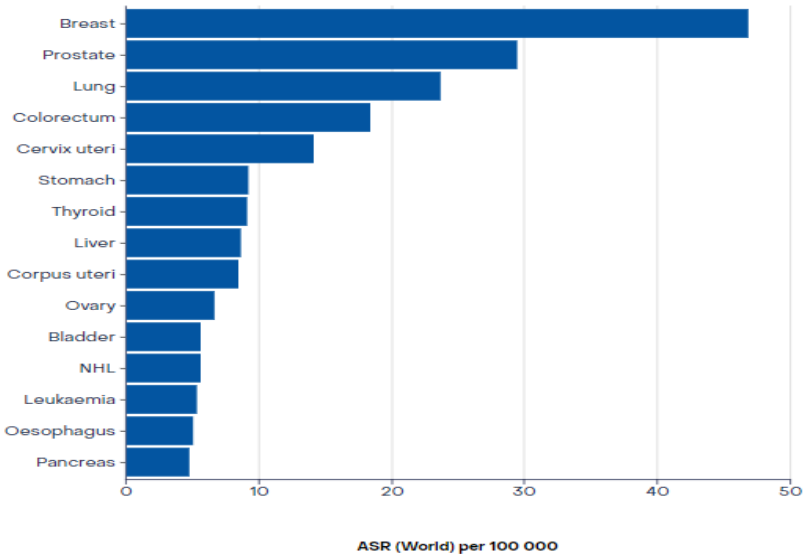

Figure 1. Breast cancer incidence rate compared to other types of cancer Source: (GLOBOCAN, 2022).

It has been shown that 5-10% of breast cancers are associated with non-modifiable risk factors such as genetic mutations and family history while 20-30% of breast cancers are associated with modifiable risk factors such as lifestyle and environmental factors. The presence of one or more of these risk factors will not necessarily lead to the development of breast cancer, thus some women carry one or more risk factors without developing the disease, while some women can develop breast cancer without carrying any of the risk factors. The reason for this is the genetic variability of individuals and the various forms of mutations they may have. In addition, the effect of the same substance varies in different people and the duration and severity of exposure plays an important role in the formation of breast cancer (Obeagu & Obeagu, 2024).

Risk Factors of Breast Cancer

Breast cancer risk factors are divided into non-hereditary and hereditary factors.

Non-Hereditary Risk Factors of Breast Cancer

Non-hereditary breast cancer risk factors are mostly related to environment and lifestyle.

Gender

The most important risk factor associated with breast cancer is being female, with 99% of breast cancer cases occurring in women. Male breast cancer is very rarely a rare disease (Yousef, 2017). Males may develop breast cancer due to many causes, including long-term exposure to radiation or a hormonal imbalance; however, the majority of male breast cancer cases are due to the BRCA2 gene mutation (Momenimovahed & Salehiniya, 2019). Male breast cancer differs from female breast cancer especially in terms of misdiagnosis and invasion. Men's lack of knowledge about breast cancer leads to late-stage diagnoses. Another reason why male breast cancer is worse than female breast cancer is that male breast tissue is thinner and tumor cells travel to the armpit and lymphatic vessels faster (Hassett et al., 2020).

Age

The incidence of breast cancer is directly proportional to age. The incidence of breast cancer peaks around age 50 due to menopause in women, but after that the rate may decrease or remain constant. However, young age is associated with a poor prognosis as the tumor appears large and at diagnosis, the lymph nodes are often positive and the recurrence rate is high (Momenimovahed & Salehiniya, 2019).

Age of Menarche and Menopause

It has been shown that women who have early menstrual periods are twice as likely to develop breast cancer compared to other women (Mao et al., 2023). On the other hand, menopause after the age of 55 also increases the risk of breast cancer (Kashyap et al., 2022). This is because women in this condition are exposed to sex hormones such as estrogen and progesterone for a long period of their lives. Late menarche or early menopause reduces the exposure of breast cells to female sex hormones and thus reduces the risk of breast cancer (Obeagu & Obeagu, 2024).

Pregnancy and Breastfeeding History

Increasing the number of births contributes to reducing the risk of breast cancer, as each birth reduces the risk of breast cancer by 10%. The reason for this is that complete lobular differentiation does not occur in women who have not given birth (Nicolis et al., 2024). The onset of breast cancer is inversely proportional to the degree of breast differentiation, with undifferentiated breasts leading to more aggressive tumors. In addition, the lack of differentiation of breast cells leads to increased susceptibility to non-estrogenic mutations and estrogen genotoxicity. Breastfeeding also increases the differentiation of breast cells, so breastfeeding for longer than 12 months reduces the risk of breast cancer (Anothaisintawee et al., 2013).

Contraceptive Methods, Ovulation-Stimulating Drugs and Postmenopausal Hormone Therapy

Despite the important role that female sex hormones and growth hormones play in the normal development of the breast and the formation of the mammary duct, exposure to high or prolonged levels of these hormones increases the risk of breast cancer (Łukasiewicz et al., 2021). Therefore, the use of birth control pills, ovulation-inducing drugs, and hormone replacement therapy for menopausal symptoms is associated with an increased risk of breast cancer (Westhoff & Pike, 2018).

Breast Diseases

Studies examining the relationship between breast disease and breast cancer are in progress. The breast can develop many diseases beyond breast cancer, such as breast cysts, fibroadenomas, and certain infections. Some breast disorders that cause breast lumps lead to health concerns associated with breast cancer. Some breast diseases may increase the risk of cancer by 4-5 times, but the association between benign breast disorders and breast cancer depends on the histologic classification of the disease and family history of breast cancer (Houghton & Hankinson, 2021).

Breast Density

The term breast density refers to the amount of dense tissue existing in the breast (Nazari & Mukherjee, 2018). Increased density of breast tissue is often associated with increased estrogen levels. Women with dense breast tissue have a higher risk of developing breast cancer than women with little or no dense breast tissue. The density of breast tissue is detected through a mammogram. Dense breasts may hide tumors because they appear white like tumors during mammography (Obeagu & Obeagu, 2024).

Smoking

Similar to all cancers, tobacco is a factor in the development of breast cancer in women who smoke. Studies have confirmed that women who smoke have a 10 times higher risk of developing breast cancer than women who non-smoke (Łukasiewicz et al., 2021). The carcinogenic effects of tobacco are caused by the presence of

aromatic hydrocarbons that lead to genetic polymorphisms in Nacetyltransferase-2 and consequently the development of breast cancer (Jones et al., 2017).

Consumption of Alcohol

Numerous studies have proven the link between alcohol consumption and an increased risk of breast cancer in women. Alcohol consumption accounts for 4% of breast cancer cases in developed countries. Studies show that ethanolic alcohol stimulates the growth of mammary epithelial cells and increases estradiol concentrations in the blood of premenopausal women.19 Ethanolic alcohol also enhances the carcinogenic effect of tobacco products and inhibits liver clearance (Łukasiewicz et al., 2021).

Obesity

Being overweight (BMI above 25 kg/m2) is a risk factor associated with breast cancer in women. Basically, estrogen is produced in the body by the ovaries, but after menopause, fat tissue produces a small amount of estrogen. More body mass means more fats tissue, which means higher estrogen levels and an increased risk of breast cancer (Tzenios, 2023). On the other hand, being overweight is associated with increased inflammation, which may increase the risk of breast cancer. In breast tissue containing excess fatty tissue, a higher dose of alcohol is metabolized into acetaldehyde, which binds to proteins and DNA and interferes with the antioxidant defense system, DNA synthesis and repair system by down-regulating BRCA1 (Vick et al., 2023).

Physical Activity

Physical inactivity is a risk factor associated with many types of cancer. Physical activity reduces the risk of chronic diseases as well as cancer and increases the chances of survival after being diagnosed with cancer (Goldschmidt et al., 2023). Physical activity supports breast cancer prevention, especially after menopause, by influencing steroid hormone metabolism, reducing inflammation, reducing body fat, improving immune system regulation, and altering the generation of free radicals. In addition, physical activity along with a balanced diet reduces the occurrence and development of genetic mutations associated with breast cancer, especially BRCA1/2 mutations (Fortner et al., 2023).

Other Factors

Several studies have demonstrated that many factors can increase the risk of developing breast cancer, such as type of diet, use of antiperspirants, stress, vitamin deficiencies, exposure to ionizers and other factors (Kashyap et al., 2022).

Hereditary Risk Factors of Breast Cancer

Many factors, including genetics, play a role in the initiation of breast cancer. Breast cancer is caused by genetic changes in the somatic cells of the breast. However, susceptibility to breast cancer may be hereditary. About 5-10% of breast tumors are hereditary, and another 15-20% are familial (Riedlova et al., 2020).

Family History and Genetic Predisposition

Personal history of breast cancer is a significant risk factor as there is an increased risk of recurrence in women who have experienced breast cancer previously. The second breast cancer may develop in the same or in a different breast. The occurrence of breast cancer among one or more close blood relatives indicates that breast cancer runs in the family (Obeagu & Obeagu, 2024). Studies have proved that the presence of breast cancer in a first-degree relative increases the risk of developing breast cancer by 2.1 times. In addition, the presence of breast cancer in the mother increases the risk by 2 times, in the sister by 2.3 times, and in the daughter by 1.8 times. If both the mother and sister have a history of breast cancer, the risk increases by 3.6 times (Açıkgöz & Akal Yıldız, 2017). Hereditary breast cancer is cancer that arises due to a genetic variation that is transmitted in an autosomal dominant manner. Breast cancer in males and breast cancer associated with cancer of the ovaries

or fallopian tubes in females is considered to be Hereditary Breast Cancer. Hereditary breast cancer was recognized as a syndrome in 1971 by Lynch and Crush. Genes associated with breast cancer risk are categorized by penetrance. Penetrance refers to the increased likelihood of breast cancer if a particular genotype is present (Mahdavi et al., 2019). In other words, penetrance means that the person carrying the mutation is susceptible to cancer (Wentzensen & Berg, 2018). Genes are divided into high, medium, and low penetrance genes according to their relative risk. High penetrance genes are associated with a relative risk of breast cancer higher than 5, and medium penetrance genes have a relative risk between 1.5 and 5. Low penetrance genes have a relative risk of less than 1.5. Accurate detection of breast cancer-associated genes can reduce the risk of cancer in susceptible people and their families (Riedlova et al., 2020).

High Penetrance Breast Cancer Genes

Highly penetrant genes are caused by mutations in a single cell or a small number of cells that lead to the formation of a pathological condition that may later turn into a malignant disease in the affected cell (Kang & Choi, 2021). Up to 25% of hereditary breast cancers are caused by a mutation in a rare but highly penetrant gene (BRCA1, BRCA2, PTEN, TP53, CDH1 and STK11). Mutations in one of these genes increase the lifetime risk of breast cancer by up to 80% (Shiovitz & Korde, 2015). The most common cause of hereditary breast cancers are BRCA1/2 genes whose mutations are inherited in an autosomal dominant manner (Naeem et al., 2019). Women who carry mutations in BRCA1 or BRCA2 are 10 to 20 times more likely to develop breast cancer than other women and are also more likely to be diagnosed with breast cancer at an earlier age. BRCA1/2 are two tumor suppressor genes by repairing double-stranded DNA breaks (Lilyquist et al., 2018). For this reason, cells carrying mutant BRCA genes are susceptible to DNA damage and genome instability and thus an increased risk of cancer (Feng et al., 2018). Males with breast cancer often carry mutations in the BRCA1 or BRCA2 gene. The most common mutations in males are BRCA2 compared to BRCA1 (Naeem et al., 2019). The TP53 gene is known as the guardian of the genome due to its important role in the process of gene regulation (McVeigh et al., 2021). The p53 protein is involved in cellular functions such as DNA repair, cell cycle control and apoptosis and therefore contributes to tumor suppression (Naeem et al., 2019). Mutations in TP53 lead to the development of multiple cancers (Li-Fraumeni syndrome) due to protein alterations, inactivation of DNA binding, or suppression of interaction with target genes (McVeigh et al., 2021). Females who carry a mutation in the P53T gene are most often diagnosed with breast cancer before the age of 30 (Bakhuizen et al., 2019). PTEN is a gene that contributes to tumor suppression by regulating PI3K and AKT signaling pathways. PTEN mutations are observed in cancer susceptibility syndromes and is the second most frequently mutated gene in human cancers after TP53. Women with Cowden syndrome who carry germline mutations in PTEN have a 50% lifetime risk of developing breast cancer (Ellsworth et al., 2019). STK11 is a gene that regulates energy metabolism and cell polarity, inhibits cellular proliferation, and interacts with the TOR pathway (Antov et al., 2017). People who carry a mutation in STK11 are susceptible to Peutz-Jeghers syndrome and various cancers, one of which is breast cancer where the lifetime risk of developing breast cancer is 24-54% (Lipsa et al., 2019). CDH1 gene is responsible for the CDH1 membrane protein that helps in the assembly of intercellular junctions and increases the adhesion of epithelial cells. Mutations in CDH1 gene lead to impaired attachment of cells to each other and to the basal membrane, which increases cell migration and invasion (Kim et al., 2016). Germline mutations in CDH1 have been associated with an increased lifetime risk of gastric and breast cancer (HDGC-syndrome) (Corso et al., 2020).

Moderate Penetrance Breast Cancer Genes

2%-3% of breast cancer cases are caused by a mutation in a moderately prevalent gene (Shiovitz & Korde, 2015). The most prominent genes with moderate penetrance are PALB2, ATM, CHEK2 and BRIP1. PALB2 is partner and localizer of BRCA2. PALB2 helps BRCA2 function because it is a key binding partner for BRCA2. In addition, PALB2 contributes to homologous recombination. PALB2 is highly associated with breast cancer and also causes aggressive clinicopathologic features (Wu et al., 2020). Breast cancer in males has been reported in male carriers of PALB2 variants (McVeigh et al., 2021). ATM is responsible for ataxia-telangiectasia syndrome and is also a gene associated with breast cancer. The ATM gene encodes a protein kinase that plays a key role in maintaining genomic stability as it acts in response to DNA damage, as well as in controlling the cell cycle and mitotic recombination (Marabelli et al., 2016). ATM gene is involved in cell cycle control, apoptosis, and gene regulation thus its dysregulation leads to many cancers such as breast cancer (Stucci et al., 2021). CHEK2 encodes a serine/threonine protein kinase. CHK2 is involved in DNA repair pathways, cell cycle regulation, and apoptosis. This gene also plays a role in the gene expression of the BRCA1/2 and TP53 genes. CHEK2 mutations are found in various types of cancer including breast cancer (Ansari et al., 2019). BRIP1

gene encodes the RecQ DEAH protein that interacts with BRCA1. In cooperation with the BRCA1 gene, the BRIP1 gene is involved in DNA damage repair and tumor suppression. Therefore, BRIP1 mutations lead to a failure to interact with BRCA1 resulting in a failure to repair damaged DNA. BRIP1 mutations have been associated with the development of tumors including breast cancer, ovarian cancer, and Fanconi anemia (Ouhti et al., 2016).

Low Penetrance Breast Cancer Genes

Gene mutations in high or medium penetrance genes are not exclusively responsible for genetic susceptibility to breast cancer; single nucleotide polymorphisms (SNPs) that may be found in the general population may also play a role in this susceptibility (Mahdavi et al., 2019). Low susceptibility alleles or modifier genes are polymorphic genes with specific alleles that are associated with altered risk of disease. In general, these variants are common in the population, and each variant can be said to be associated with only a small increase in an individual's breast cancer risk. However, the risk of these variants in the population as a whole is higher than rare, highly prevalent susceptibility genes (Ozgoz et al., 2020). Several susceptibility variants related to breast cancer were determined via genome-wide association studies (GWAS). GWAS is a dedicated research strategy to determine genetic correlations between genetic polymorphisms and diseases, traits, or variation (Mahdavi et al., 2019). Some variants in MSH2, MLH1, CYP1A1, NAT2, CAG, TGF-β1, LGR6, MDM4, TERT, ESR1, TOX, CASP8, MAP3K1, LSP1, FTO, FGFR2, RAD51C, RAD51D, MRPS30, COX 11 and SLC4A7 can all be considered low-penetrance genes for breast cancer. Further studies are still ongoing to identify more variants in other genes that are associated with breast cancer risk.

MicroRNAs (miRNAs)

Breast cancer susceptibility genes are not the only genetic factor that increases the risk of breast cancer. There are other genetic factors that play a role in increasing the risk of breast cancer such as miRNAs (Ellsworth et al., 2019). miRNAs are a group of non-protein-coding, endogenous, single-stranded and small RNAs that alter genetic expression through binding to messenger RNA (mRNA) domains and decreasing transcription or promoting mRNA degradation. Polymorphisms inside a germ line can lead to the removal or creation of mRNA binding domains or alter the specific functionality of the mRNA (Cardinali et al., 2022). Cancer-associated regions comprise approximately 50% of miRNAs -encoding genes. In addition, about one-third of protein-coding genes in humans are regulated by miRNAs. Thus, dysregulation of miRNAs can lead to the development in human cancers such as breast cancer. There are two types of miRNAs associated with breast cancer: Oncogenic miRNAs (oncomiRs) and tumor suppressor miRNAs (tsmiRs) (Loh et al., 2019). When oncomiRs overexpression occurs, breast cancer arises and the likelihood of cancer cell migration increases. This is because overexpression of RNA leads to suppression of the expression of tumor suppressor genes (e.g., miR-10b targeting E-cadherin, miR-21 targeting PDCD4, miR-155 and miR-27b targeting ST14). In contrast, tsmiRs inhibit the expression of some oncogenes, and therefore a decrease in their expression may lead to the development of breast cancer (e.g., miR-26b which reduces the expression of FOXM1 and miR-26b which targets CDK8) (Yang & Liu, 2020).

Mitochondrial DNA (mtDNA)

Mitochondria are involved in energy metabolism, cell proliferation, senescence, and apoptosis. Mitochondria contain their own circular DNA termed mitochondrial DNA (mtDNA). mtDNA contains 22 tRNA, 2 rRNA and 13 genes that encode the protein subunits of the mitochondrial complexes of the oxidative phosphorylation system (Weerts et al., 2019). The mtDNA content of each cell is constants but certain factors such as exposure to toxins, viral infections, and genetic mutations can lead to changes in it (Weerts et al., 2016). Genetic variants and oncogenic mutations in mtDNA may lead to the development of breast cancer (Weerts et al., 2019). In other words, low mtDNA gene expression or mtDNA mutations increase the risk of developing breast cancer as mtDNA mutations are found in 60% of breast tumors (Pérez-Amado et al., 2020).

Results and Discussion

Breast cancer is the most common cancer among women in both developed and developing countries. Several factors increase the risk of developing breast cancer. Identifying factors that increase the risk of breast cancer

contributes to increasing effective screening practices for individuals at risk and therefore reducing the incidence of breast cancer. Breast cancer risk factors are generally divided into two groups: hereditary and non-hereditary. Age, gender, lifestyle, harmful use of alcohol and tobacco, reproductive history, and use of hormone therapy are among the non-hereditary factors. Therefore, modifying lifestyle and daily habits may help reduce the incidence of breast cancer. However, women can develop breast cancer even though they do not carry any of the non-hereditary risk factors. This is because they may carry hereditary risk factors such as genetic mutations and a family history of the disease. Hereditary risk factors are unchangeable. Thus, women with a family history of breast cancer are advised to undergo genetic testing for counseling. Although not all women with breast cancer risk factors will develop breast cancer, knowing and studying risk factors is helpful in prevention.

Recommendations

Despite much research investigating the risk factors for breast cancer, many factors still need to be examined. Hereditary breast cancer risk factors are the most serious because they are often not amenable to lifestyle or environmental changes. Therefore, we recommend further research to identify hereditary breast cancer risk factors and the possibility of finding ways to help prevent breast cancer in individuals who are carriers of these risk factors.

Scientific Ethics Declaration

* The authors declare that the scientific ethical and legal responsibility of this article published in EPHELS Journal belongs to the authors.

Conflict of Interest

* The authors declare that they have no conflicts of interest

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