Mini Review

CLINICAL INVESTIGATION

Breast cancer risk factors and preventative measures: A Review

Abstract

Breast cancer is the second largest cause of mortality among women from cancer. Breast cancer is a multi-step process involving various cell types, and prevention is still difficult around the world. One of the most effective ways to avoid breast cancer is to diagnose it early. Breast cancer patients in some developed nations have a 5-year relative survival rate of more than 80% due to early detection and treatment. Great strides have been achieved in the understanding of breast cancer and the development of prevention strategies in the last decade. Breast cancer stem cells have disclosed the aetiology and tumour drug-resistant mechanisms, and numerous genes related to breast cancer have been discovered. People now have more pharmacological alternatives for breast cancer chemoprevention, and biological prevention has recently been created to improve patients' quality of life. We will outline major studies on pathogenesis, associated genes, risk factors, and preventative strategies on breast cancer that have been published in recent years in this review. These findings are an important step forward in the ongoing battle against breast cancer.

Keywords: breast cancer • prevention • pathogenesis • risk

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Jennifer Stewart*

Editorial Office, Journal of Clinical Investigation, London

*Author for correspondence: clinicalinvestigation@escienceopen.com

Introduction

Breast cancer is one of the most frequent malignancies in women worldwide, with 570,000 fatalities reported in 2015. Every year, about 1.5 million women worldwide (25% of all cancer patients) are diagnosed with breast cancer. Breast cancer is predicted to account for 30% of all new cancer cases in women in the United States (252,710) in 2017. Breast cancer is metastatic cancer that can spread to distant organs such as the bone, liver, lung, and brain, making it nearly impossible to cure. An excellent prognosis and a high survival percentage can be achieved if the disease is detected early. Breast cancer patients in North America have a 5-year relative survival rate of more than 80% due to early identification of the disease. Mammography is a frequently used screening method for detecting breast cancer that has been shown to effectively reduce mortality. Other screening modalities, like MRI, which is more sensitive than mammography, have also been used and explored throughout the previous decade. Many factors, including sex, ageing, oestrogen, family history, gene mutations, and an unhealthy lifestyle, might raise the risk of getting breast cancer. The majority of breast cancer instances occur in women, and the number of cases in women is 100 times higher than in males. Even though the incidence of breast cancer in the United States rises year after year, the mortality rate falls as a result of widespread early detection and better medical treatments. Biological therapy for breast cancer have been discovered in recent years and have shown to be effective. In this section, we'll look at recent research on the pathophysiology, linked genes, risk factors, and preventions of breast cancer [1].

Breast cancer related genes

BRCA1 and BRCA2 (Breast Cancer Related Gene 1 and 2) are two well-known anti-oncogenes linked to breast cancer risk. BRCA1 and BRCA2 are found on the 17th and 13th chromosomes, respectively. Both of these genes code for tumour suppressor proteins. BRCA1 loss causes cell cycle checkpoint dysregulation, aberrant centrosome duplication, genetic instability, and ultimately apoptosis. In an E2F-dependent way, "pocket proteins" such as p130, p107, and the retinoblastoma protein suppress BRCA1 expression. The BRCA1 gene has been demonstrated to form a loop between the promoter, introns, and terminator regions that regulates the gene's expression through interactions with its own promoter. By interacting with RAD51 and DMC1, the BRCA2 protein governs re-combinational repair in DNA double-strand breaks. High-grade invasive ductal carcinomas with a luminal phenotype are more common in BRCA2-associated breast cancers [2,3]. If a person inherits

detrimental mutations in the BRCA1 or BRCA2 genes, their risk of breast cancer could skyrocket. Even when the second allele is normal, BRCA1/2 mutations are inherited in an autosomal dominant manner. BRCA1/2 mutations cause about 20%-25% of hereditary breast cancers and 5%-10% of all breast cancers. Chen found that women over 70 years old with BRCA1 or BRCA2 mutations had a risk ratio of 57% and 49%, respectively, in a meta-analysis.

Epidermal Growth Factor Receptor (EGFR)

In humans, EGFR is found on the short arm of chromosome 7, commonly known as c-erbB-1 or Her1 (7p12). The EGFR protein is a tyrosine kinase family cell surface glycoprotein that is activated by binding to EGF, TGF-, amphiregulin, betacellulin, and other proteins. EGFR's downstream signalling pathways, including as PI3K, Ras-Raf-MAPK, and JNK, are activated to increase cell proliferation, invasion, and angiogenesis while also protecting cells against death. More than 30% of instances of Inflammatory Breast Cancer (IBC), an extremely aggressive subtype of breast cancer, had EGFR overexpression [4]. EGFR-positive IBC patients had a worse prognosis than EGFR-negative IBC patients. EGFR overexpression is found in more than half of Triple-Negative Breast Cancer (TNBC) patients, which are defined by the absence of Estrogen Receptor (ER), Progesterone Receptor (PR) expression, and HER2 amplification. As a result, blocking the EGFR pathway could be a promising treatment option for these cancerous tumors.

Human epidermal growth factor receptor 2

Human epidermal growth factor receptor 2, commonly known as c-erbB-2, is a breast cancer oncogene that is found on human chromosome 17's long arm (17q12). Neu, which was first discovered in 3-methylcholanthrene-induced rat neuroblastoma cells, is the homologene in mice. Gene amplification and re-arrangement are the primary mechanisms by which the HER2 gene is activated. The HER2 protein is a tyrosine kinase member of the epidermal growth factor receptor (EGFR) family that forms heterodimers with other ligand-bound EGFR family members including Her3 and Her4 to activate downstream signalling pathways. In mouse models, knocking down HER2 causes mammary duct development to be disrupted. PTEN/Akt/mTORC1 signalling increases the number of cancer stem cells, which suggests poor clinical outcomes. Overexpression of HER2, which is found in roughly 20% of initial breast tumours, increases the number of cancer stem cells and implies poor clinical outcomes [5].

Ras gene

The Ras gene family consists of three members: H-ras, K-ras, and N-ras, which are found on chromosomes 11 (11p15), 12 (12p12), and 1 (1p22), respectively. The tiny guanosine triphosphate (GTP)-binding protein (G protein) superfamily contains the proteins encoded by these genes, which are very similar. Overexpression of these three human Ras genes is frequently linked to point mutations, the majority of which are missense mutations in the GTP binding coding domain. Though Ras protein mutations are uncommon in breast cancer (5%), abnormalities in the Ras signal transduction system can be seen in both benign and malignant mammary tissues. In breast cancer cells, H-ras can work together with B lymphoma moloney murine leukaemia virus insertion region-1 (BMI1) to increase proliferation, invasion, and block apoptosis. Both primary and metastatic breast cancer patients have H-ras overexpression, which indicates a bad prognosis [6,7].

Factor of Risk

History of family

Family history is linked to about a quarter of all breast cancer cases. Breast cancer is more likely in women whose mother or sibling has the disease. Those with one first-degree family with breast cancer have a 1.75-fold higher chance of having the disease than women without any affected relatives, according to a cohort study of nearly 113,000 women in the United Kingdom. Furthermore, women with two or more first-degree relatives with breast cancer face a 2.5-fold or higher risk. Breast cancer susceptibility is inherited in part due to mutations in breast cancer-related genes such as BRCA1 and BRCA2.

Lifestyle

Excessive alcohol consumption and a high dietary fat intake are two modern lifestyle factors that can raise the risk of breast cancer. Alcohol consumption can cause an increase in estrogen-related hormones in the bloodstream, as well as the activation of estrogen receptor pathways. According to a meta-analysis based on 53 epidemiological studies, drinking 35grams-44 grams of alcohol per day increases the risk of breast cancer by 32%, with each extra 10 grams of alcohol per day increases the risk by 7.1%. Excess fat intake, particularly saturated fat, is linked to mortality (RR=1.3) and poor prognosis in patients with breast cancer in the modern western diet [8]. Although the link between smoking and breast cancer risk is still debated, mutagens from cigarette smoke have been found in non-lactating women's breast fluid. Breast cancer risk is also increased in women who smoke and drink (RR=1.54). Until now, mounting data has shown that smoking, especially when started at a young age, increases the risk of breast cancer.

Reproductive factors

Breast cancer risk can be increased by reproductive variables such as early menarche, late menopause, late age at first pregnancy, and low parity. Each year that menopause is postponed increases the risk of breast cancer by 3%. Breast cancer risk is reduced by 5% to 10% for every year that menarche is postponed or for each additional birth. The Hazard Ratio (HR) between late (35 years) and early (20 years) age at first birth is 1.54, according to a recent Norwegian cohort research. Reproductive variables are highly linked to ER status, with variations in the odds ratios (OR) for parity (0.7 *vs.* 0.9 for 3 births vs. nulliparae) and age at first birth (1.6 *vs.* 1.2 for age 30 *vs.* 25 years) between ER+ and ER- breast cancer.

Preventions

Biological prevention

Tumour metastasis, not primary tumours, is responsible for approximately 90% of cancer fatalities. If breast cancer is detected as a primary tumour or at an early stage of metastasis, the breast tumour can be surgically removed and chemotherapy can be administered effectively. The cornerstone of breast cancer prevention is early detection. Mammography is a screening technique that uses low-energy X-rays to produce high-resolution images of the breast. The complete procedure takes about 20 minutes and does not involve the use of any contrast-enhancing agents. Since Professor Forrest's original advice for breast cancer screening, over 70% of American women (aged 50 years-74 years) have had their breasts screened every two years with mammography. A meta-analysis of 11 randomized trials found that screening with mammography reduced breast cancer mortality in women aged 50 years to 70 years (RR=0.81). In women aged 40-49 years, however, the drop in death rate was not substantial. These findings highlight the value of mammography screening programs [9,10]. Although the rate of overdiagnosis due to mammography varies between studies, it is undeniably a severe issue that should not be overlooked during breast cancer screening. Another extensively used breast cancer screening method is Magnetic Resonance Imaging (MRI). In high-risk women, it is more sensitive than mammography, especially in finding invasive ductal carcinoma. When compared to mammography, MRI offers an advantage in detecting occult primary breast cancer, axillary nodal metastasis, residual tumours after neoadjuvant treatment, and other small tumours. Tissues as tiny as 0.5 mm3 can be measured using advanced MRI scanners. However, there is no evidence that MRI improves patient outcomes such as the rate of detecting ipsilateral breast tumour recurrence or the incidence of contralateral breast cancer. MRI has substantially lower specificity than mammography, with detection rates ranging from 37% to 100%. According to MRI screening, women with a family history of breast cancer have a lifetime risk of breast cancer of 20%-25% or higher. Each coin has two sides, and we must strike a balance between the good and the bad. When mammography results are normal, MRI may be a good option in high-risk groups because of its sensitivity.

Screening

Biological prophylaxis, primarily monoclonal antibodies for breast cancer, has recently been created to improve the quality of life of breast cancer patients. HER2 is one of the primary targets of these monoclonal antibodies. HER2 protein overexpression or HER2 gene amplification is found in 20%-30% of all breast cancer patients. The first HER2-targeted medicine to be authorized by the FDA is trastuzumab (Herceptin), a recombinant humanized monoclonal antibody. It can connect directly with the C-terminal portion of domain IV in HER2's extracellular region.

Chemoprevention

Trastuzumab's anti-tumour mechanism has not been fully understood to date. Trastuzumab may decrease cancer cell growth and proliferation by recruiting ubiquitin to internalise and degrade HER2, activating the immune system against cancer cells through a mechanism known as Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC), or blocking the MAPK and PI3K/Akt pathways. Trastuzumab was first used to treat Metastatic Breast Cancer (MBC), and it was found to be effective as a single agent, with a 26% Objective Response Rate (ORR). Trastuzumab has a synergistic impact with other anti-tumour medications such nimotuzumab, carboplatin, 4-hydroxycyclophosphamide, docetaxel, and vinorelbine, according to in vitro studies. Marty also conducted a randomised phase II trial that found that trastuzumab with docetaxel was more effective than docetaxel alone in treating HER2-positive MBC, with an ORR of 50% versus 32%. Trastuzumab-treated patients, on the other hand, experienced side effects such as congestive heart failure and a decrease in Left Ventricular Ejection Fraction (LVEF). Pertuzumab (Perjeta), a humanised monoclonal antibody that works similarly to trastuzumab, can bind to the extracellular region of HER2. The binding domain, on the other hand, is different. The combination of pertuzumab, trastuzumab, and docetaxel has been approved for the treatment of HER2-positive breast cancer. In HER+ tumours, the rate of Pathologic Complete Response (pCR) and invasive-disease-free survival was considerably higher than in HER- tumours (57.8% versus 22.0%). In the pertuzumab-treated groups, however, severe side events such as diarrhoea and febrile neutropenia were prevalent. Immunotherapy has recently been a trendy topic in cancer treatment, and it has shown considerable promise in clinical trials. Programmed Cell Death 1 (PD1) is a membrane protein found in a variety of immune cells, including T cells, which can be activated by a specific ligand to prevent the immune system from functioning properly. Nivolumab (Opdivo) and Pembrolizumab (Keytruda), PD1 inhibitors, have been licenced for the treatment of a variety of solid cancers, including metastatic melanoma and non-small cell lung cancer. Pembrolizumab was found to be successful in 27 TNBC patients in the KEYNOTE-012 study, with a clinical benefit rate of 20%. PDL1, a ligand of the programmed cell death receptor 1, is found in 20% of TNBC and 50% of all breast tumours. In a phase I research including 54 TNBC patients, the PDL1 inhibitor medication Atezolizumab (Tecentriq) showed a 19% objective response rate. Even though TNBC patients have a dismal prognosis, anti-PD1/PDL1 medicines could be a viable treatment option for this subtype of breast cancer.

Conclusion

The study showed the prevention and risk of breast cancer. Different prevention factors have been used in this study.

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