International Journal of New Findings in Health and Educational Sciences (IJHES)
ISSN 2980-0641
DOI : 10.63053/ijhes.23

Breast Cancer, a Global Health Crisis

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ARTICLE INFO

Keywords:
Breast Cancer,
Young Women,
Mammography
, Pregnancy,
BTBD7

ABSTRACT

Breast cancer is still a public health problem worldwide and is currently the most common tumor in the world. Breast cancer is a life-threatening disease in women and the leading cause of death in the female population. Breast cancer is a heterogeneous disorder with different molecular subtypes and biological characteristics, with different therapeutic functions and clinical outcomes for each molecular subtype. Furthermore, the treatment of BC is complicated by intratumoral complexity. Consequently, breast cancer risk assessment is an important part of public health. Precision medicine for breast cancer is a practice for diagnosis, treatment, screening and prevention of the disease that takes into account the patient's genetic makeup. Therefore, by identifying women who are at high risk of breast cancer, it is possible to make personalized recommendations regarding screening methods, the age at which breast screening should begin, the frequency of completing screenings, and individual counselling.

Introduction

Breast cancer (BC) is the second leading cause of cancer-related death in women under the age of 40 worldwide. In addition, the incidence of breast cancer in young women (BCYW) is increasing. Young women are not the focus of screening programs and BC is diagnosed in younger women at more advanced stages. Such patients have worse clinical outcomes and treatment complications compared to older patients (Jie Wei Zhu et al, 2023). Breast cancer arises from the accumulation of genetic and somatic mutations that lead to increased uncontrolled cell division and proliferation. Activating mutations in more than 30 cancer genes have been implicated in breast cancer, including AKT1, BRCA1, CDH1, GATA3, PIK3C, PTEN, RB1 and TP53 (Basmadjian et al, 2023). The risk of breast cancer is affected by many factors including age, family history, fertility history, hormonal exposure (use of combined estrogen and progestin hormone therapy after menopause), use of oral contraceptives, proliferative breast lesions, activity Physical, alcohol consumption, tobacco use, exposure to ionizing radiation, breast density, and environmental exposures possibly associated with breast cancer include dioxins and air pollution. The most important risk factor for breast cancer is age. The risk of breast cancer increases after the age of 20 to the age of 85. Breast cancer is predominantly a female disease. While about 0.1% of men get breast cancer during their lifetime (Hipp et al, 2022).

Hereditary breast cancer

Genetic evaluation is an essential component of multidisciplinary care for AYAs with breast cancer and should begin immediately after diagnosis. Patients need both pre-test counseling to assess family history and risk assessment, and post-test genetic counseling to accurately interpret test results and medical examination. Because multiple genes may predispose AYAs to early breast cancer. , next-generation sequencing panels – which assess and express multiple genes simultaneously – are superior to single-gene testing. Women with familial breast cancer syndromes need individualized counseling, annual screening, evidence-based recommendations on tumor surveillance and preventive mastectomy/oophorectomy, ongoing support for decision-making, and lifelong tumor surveillance (Johnson et al, 2018).

Breast cancer during pregnancy

The incidence of breast cancer in pregnancy is approximately 1 in 3000 and can reach up to 3%. The prevalence of pregnancy-related breast cancer may be increasing due to delayed childbearing, and despite its low incidence, breast cancer is the second most common cancer in pregnant women. Women who have their first child after age 30 have a slightly higher risk of breast cancer than women who are typically exposed to higher levels of estrogen over a long period of time. Early menstruation (before the age of 12) and menopause after the age of 55 are also important risk factors. Cyclical hormone levels also predispose women to breast cancer over time. And it may be because breast cells multiply, grow, and divide in response to hormones such as estrogen, and pregnancy leads to an interruption in normal cyclic hormone levels (Polivka Jr et al, 2018). Breast cancer in pregnancy often presents as a painless lump or thickening in the breast, which is sometimes accompanied by discharge from the nipple. Normally, the average breast weight during pregnancy increases from 200 grams to 400 grams, that is, it doubles, and as a result, the stiffness and density of the breast increase, which makes the interpretation of the results of clinical examination and mammography more challenging. Breast hypertrophy and enlargement may make physical examination and mammography imaging more difficult in pregnant patients than in non-pregnant patients. Initial screening may be done in non-pregnant women. However, for pregnant women, special attention should be paid to the risks of ionizing radiation exposure to the fetus

(Durrani et al, 2018). Pregnancies complicated by breast cancer are at increased risk for preterm labour as well as premature rupture of membranes (PPROM). Also, stillbirths have been observed in pregnancies complicated by PABC. Currently, there is limited information on the underlying reasons for the higher prevalence of preterm birth and other adverse obstetric/fetal/neonatal outcomes in breast cancer-complicated pregnancies. It can be assumed that such complications may be a direct effect of the time and type of treatment (mostly chemotherapy). Early neonatal complications include neonatal death, admission to the neonatal intensive care unit (NICU), blood disorders (especially neonatal anemia), low birth weight, and other abnormalities and disorders related to prematurity (respiratory distress syndrome, metabolic disorders, sepsis, neonatal jaundice and enterocolitis) (Margioula-Siarkou et al, 2023).

Fetal/neonatal complications associated with PABC treatment

Prescribing chemotherapy in the second and third trimesters of pregnancy is safe and acceptable for patients with PABC, but it is contraindicated in the first trimester due to the high risk of fetal abnormalities. Before starting any oncological treatment, fetal ultrasound should be performed to rule out the presence of previous abnormalities that could be mistakenly attributed to maternal treatment. In case of accidental administration of chemotherapy regimens during the first trimester, the risk of spontaneous abortion and congenital malformations increases significantly (14-19%), because the organogenesis of the fetus during this period can be strongly affected by cytotoxic agents. be disturbed Transient hematologic toxicity and myelosuppression of the fetus are rare but potentially serious neonatal complications of chemotherapy exposure. To avoid this risk and subsequent hematologic complications during delivery, such as haemorrhage, sepsis, or death, at least a 3-week interval between the last chemotherapy dose administration and delivery is recommended to allow the fetal bone marrow to recover. and reduce the risk (Maggen et al, 2020).

Fetal exposure to radiation can also have adverse consequences that vary depending on gestational age and radiation dose. In general, radiation doses below 0.1–0.2 Gy are considered safe for the embryo, exposure to higher doses during the first two weeks after fertilization is likely to result in failure of blastocyst implantation.

Exposure to radiation 2 to 8 weeks after conception may cause fetal disorders and abnormalities in developing organs, particularly the central nervous system. which is significantly sensitive to radiation, with reduced intelligence quotient (IQ) and mental retardation recognized as potential long-term adverse outcomes (Alfasi and Ben-Aharon et al, 2019). The risk of fetal complications associated with radiation therapy decreases significantly after 25 weeks of pregnancy. While proper protection of the fetus during radiation therapy is required to reduce the exposure of the fetus to scattered radiation. In general, radiation therapy is not considered as a treatment option for pregnant patients with PABC, but for patients with PABC after delivery (Ramesh et al, 2019).

Breast cancer and stress

Emotional stress is believed to be associated with increased tumour progression. Behavioural studies have shown that persistent emotional distress can change the psychological and physiological characteristics of cancer patients, especially breast cancer patients. Conventional cancer treatments also compromise the quality of life of cancer patients and also have side effects. And they can provoke factors such as nervous and mental disorders, chronic depression, anxiety and insomnia. Emotional stress can increase the aggressiveness, division, and proliferation of tumours in several cancers, including breast cancer. Persistent stress can over-activate the hypothalamic-pituitary-adrenal (HPA) axis, disrupt the circadian rhythm, and dysregulate the immune response, which can ultimately exacerbate several cancers and metastases.

help. It has been found that not only genetic predisposition but also epigenetic changes play a very important role in cancer

(Fiaz et al, 2022). Emotional stress may be one of the factors that can accelerate metastasis through epigenetic methods. Genes related to stress in breast cancer include OXTR, NR3C1, -HTT 5, and FKBP5 (Peng et al, 2018).

BTBD7: a double-edged sword in breast cancer

BTB/POZ domain-containing protein 7 (BTBD7) has a relative molecular weight of 126KD and contains two conserved BTB/POZ protein sequences. BTBD7 has been shown to play an essential role in normal human development, cell growth, precancerous lesions, heat stress response, and tumour progression. BTBD7 has also been found to play an important role in cancer. High expression of BTBD7 affects tumour progression by regulating multiple pathways of BTBD7. SLUG plays an important role in the morphogenesis of epithelial branching and the invasion and division of tumour cells. Acts as an essential transcription factor regulating EMT Zi-Xiong Li. et al found: SLUG and EMT expression can be suppressed by silencing BTBD7 and tumour progression can be inhibited.

Furthermore, by studying common tumor signalling pathways, the researchers found that only the Wnt signalling pathway was significantly suppressed after BTBD7 knockdown and that the Wnt signalling pathway is commonly associated with invasive metastatic effects of tumours.

Is. β-catenin is a critical protein in the classical Wnt signalling pathway (i.e. Wnt/β-catenin signalling pathway)

(Liu et al., 2023).

Therefore, Li Jun et al. found that the loss of the BTBD7 gene prevented the activation of the Wnt/β-catenin signalling pathway and inhibited the metastatic capacity and proliferation of MCF-7 human breast cancer cells. Similarly, Notch signalling has been shown to play an important role in breast cancer progression. BTBD7 affects the Notch signalling pathway and BTBD7 can prevent cell proliferation and division, invasion and migration by suppressing Notch1 signalling in breast cancer (Li Li et al, 2018).

In breast cancer resistance studies, researchers have found that extracellular vesicles can regulate EMT and promote tumour angiogenesis and resistance to chemotherapy (Namee and O' Driscoll, 2018). MiR-887-3p (MiR-887-3p) is a microRNA and It is widely considered as a promising biomarker for drug resistance in breast cancer.

BTBD7 is a target gene of miR-887-3p. Furthermore, in related experiments, MDA-MB-231-derived extracellular vesicles were found to transport miR-887-3p to breast cancer cells and inhibit BTBD7 expression. This process activates the Notch1/Hes1 signaling pathway, which increases drug resistance in breast cancer cells. The role of BTBD7 in human breast cancer needs to be better understood for the accurate detection of breast cancer and any therapeutic function for breast cancer. Therefore, the use of BTBD7 may be a promising way to treat breast cancer (Wang et al, 2022).

Diagnostic methods

Scientific research aimed at studying the pathogenetic mechanisms and clinical consequences of cancer has always been and still is strongly focused on breast cancer. Certainly, scientific advances have been significant in recent years, but despite this, breast cancer remains the most common cause of cancer in women, putting younger women at greater risk. Mammography and ultrasound were recognized as the most useful and effective diagnostic techniques for women with non-dense and dense breast tissue, respectively. In addition, breast self-examination, magnetic resonance imaging, high-quality digital mammography, spectral contrast mammography, optical mammography, radiothermometric mammography, scintimammography, and positron emission tomography helped in the early detection of tumors or tumor-prone lesions. Therefore, along with the progress in diagnosis, genomic studies, genomics and the identification of new biomarkers have enabled the implementation of effective precision medicine (Albi et al, 2023).

Comparison of methods:

Ultrasound alone is not an acceptable or valid screening tool in young women, but it is the preferred imaging modality in pregnant and symptomatic women under 30 years of age. If more examinations and tests are needed, digital mammography is preferable to film mammography in dense breasts and is more sensitive in young patients. New mammography techniques such as tomosynthesis may be promising, especially in detecting dense breast malignancies in young women (Kudela et al, 2019).

Compared to mammography, magnetic resonance imaging (MRI) is not affected by breast density and is more sensitive in evaluating tumor location and size and evaluating multifocal lesions. However, mammography screening of women at higher risk should start earlier (Monticciolo et al, 2018).

treatment

Use of liquid biopsy to aid drug selection

Most patients with early breast cancer can have a reasonable rate of cure through surgery combined with radiotherapy and chemotherapy, while some may not be cured. It has been found that the poor results of breast cancer treatment are often related to its drug resistance (Liu et al, 2023).

Drug resistance has become the biggest obstacle to the success of cancer treatments and accounts for more than 90% of the deaths of cancer patients, who receive traditional chemotherapy and radiation therapy or new targeted drugs. Resistance mechanisms include increased metabolism of xenobiotics, increased drug flow, growth factors, increased DNA repair capacity, and genetic factors (genetic mutations, amplifications, and epigenetic changes). LB (Liquid Biopsy) can be used to determine the most effective and accurate treatments and may be a promising non-invasive method. With research advances, it is possible to predict therapeutic response to drug therapy based on LB (Freitas et al, 2022).

For example, Di Cosimo et al found that increased miR-148a-3p and miR-374a-5p in blood were associated with a pathologic complete response (pCR) after trastuzumab-based neoadjuvant therapy, suggesting that these miRNAs can be used as predictive biomarkers (Di Cosimo et al, 2020). Another study confirmed that miR-503 was increased in the plasma of patients with BC (breast cancer) after neoadjuvant treatment, which resulted from the upregulation of exosomes released from endothelial cells after treatment with paclitaxel and epirubicin (Bovy et al., 2015). This miRNA may contribute to the direct effects of taxane and anthracycline treatment and can be used as a predictive biomarker (O'Leary et al, 2018).

Treatment of triple negative breast cancer

Triple negative breast cancer (TNBC) is a heterogeneous group of tumors, which includes different breast cancers. which are simply characterized by the lack of estrogen receptor, progesterone receptor and overexpression of human epidermal growth factor receptor 2 gene (Derakhshan et al, 2022).

TNBC accounts for 10-20% of all invasive breast cancers. and includes more than one molecular subtype of TNBC. It is an aggressive phenotype that has a poorer prognosis than ductal tumors. and characterizes a stable subgroup of breast cancer with heterogeneous clinical manifestations, behavior, pathology and response to treatment. Apart from invasive ductal cancer, medullary, metaplastic, secretory, lobular pleomorphic, adenoid cystic carcinoma, etc. also belong to triple negative tumors. The main features of triple negative breast cancer include the following:

1) It is often seen in younger women (less than 50 years old)
2) It occurs more in African-American women and black people
3) It usually occurs in the form of distant cancers
4) They have high chemical sensitivity
5) weak correlation between tumor size and lymph node metastasis
6) more aggressive with the possibility of brain metastases and high recurrence probability in the first and third year after diagnosis
7) Compared to other subtypes, they have a shorter survival after the first metastatic site

TNBC usually presents at an age younger than the age at which organized breast cancer screening programs are received, and therefore most patients present with a palpable tumor. Among women who undergo regular breast cancer screening, TNBC is usually seen as an interval cancer (between

two mammograms). Patients with TNBC usually have unfavorable histopathological features with higher grade, larger tumor size and lymph node positivity (Kumar and Aggarwal, 2016).
In addition, there are limited systemic treatment options for triple negative breast cancer (TNBC) (Kwapisz, 2021). Consequently, the treatment of TNBC remains challenging. Because it is the most resistant subtype of breast cancer to treatment. Induction of ferroptosis is a therapeutic strategy that can be investigated. Because TNBC is a tumor rich in iron and fat. Coordination between metabolic pathways in the regulation of ferroptosis offers a novel therapeutic approach for TNBC. Ferroptosis is a non-apoptotic, iron-dependent form of cell death that culminates in severe lipid peroxidation in metabolic dysfunction.
Cell death via ferroptosis by peroxidation of phospholipidOxPE (oxidized phosphatidylethanolamine), a process catalyzed by lipoxygenases. And relying on metallic iron, reactive oxygen species (ROS) and phospholipids containing PU (PE) unsaturated fatty acids complete the process (Zhang et al., 2023).
Triple-negative breast cancer has heterogeneous phenotypes in ferroptosis-related metabolites and metabolic pathways. The luminal androgen receptor (LAR), a subtype of TNBC, was shown to regulate oxidized phosphatidylethanolamines and glutathione metabolism in particular (GPX4), allowing the use of GPX4 inhibitors to induce ferroptosis.
In addition, GPX4 inhibition not only induces tumor ferroptosis, but also enhances antitumor immunity. A combination of GPX4 inhibitors and anti-PD1 has more therapeutic efficacy than monotherapy. However, recent ferroptosis research in breast cancer has focused mainly on identifying novel molecules that regulate ferroptosis
(Yang et al., 2023).

Metastatic breast cancer

The MBC process is a complex multi-step process. which includes many stages of communication between tumor cells and the host, which leads to the exit of tumor cells from the primary site and metastasis to distant areas. During the early stages of tumor growth, proliferation, and division, the host activates tissue repair mechanisms by providing the neoplasm with a vascularized source of nutrients, removal of waste products, and an escape route for the potential metastatic cell in an attempt to compensate for changes at the primary site
(Miglietta et al., 2022).
However, medicinal agents and treatment methods (chemotherapy, gene therapy, hormone therapy, immune therapy and surgery) are used to treat MBC. The combination of several treatment methods and the simultaneous use of drugs can improve the patient's quality of life (Al-Mahmood et al, 2018).

Conclusion:

Breast cancer screening is an effective measure to prevent and detect the disease in the early stages and improve the survival rate of cancer patients. Screening guidelines can provide valuable tools for clinical decision-making by reviewing available evidence and making recommendations (Cardoso et al, 2019). Most of the guidelines issued by developed countries contain almost identical but not identical recommendations for breast cancer, regarding age, methods, time and intervals of screening. Most guidelines recommend annual or biannual screening mammography for intermediate-risk populations between 40 and 74 years of age and annual primary MAM or annual MRI for high-risk populations, including those with hereditary breast cancer (Ren et al. , 2022).

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