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Breast Cancer: A Review of Risk Factors

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ABSTRACT

Breast cancer is the second leading cause of cancer deaths among women. The development of breast cancer is a multi-step process involving multiple cell types, and its prevention remains challenging in the world. Early diagnosis of breast cancer is one of the best approaches to prevent this disease. Currently, people have more drug options for the chemoprevention of breast cancer, while biological prevention has been recently developed to improve patients' quality of life. In this review, we will summarize key studies of pathogenesis, related genes, risk factors and preventative methods on breast cancer over the past years. 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.

Keywords: risk factors, breast cancer, prevention, cancers

INTRODUCTION

Breast cancers is one of the common and multiple malignant tumours in women. The occurrence and development of breast cancer is the result of a combination of factors inside and outside the body [1-3]. Its occurrence is associated with poor lifestyle factors, environmental factors, and social psychological factors. It has been shown that 5–10% of breast cancers can be attributed to factors such as genetic mutations and family history, and 20–30% of breast cancers can be attributed to potentially modifiable factors [4]. Breast cancer starts in the cells of the breast. A cancerous tumour is a group of cancer cells that can grow into and destroy nearby tissue. It can also spread to other parts of the body. Cells in the breast sometimes change and no longer grow or behave normally. These changes may lead to non-cancerous breast conditions such as atypical hyperplasia and cysts. They can also lead to non-cancerous tumours such as intraductal papillomas [5]. But in some cases, changes to breast cells can cause breast cancer. Most often, breast cancer starts in cells that line the ducts, which are the tubes that carry milk from the glands to the nipple. This type of breast cancer is called ductal carcinoma. Cancer can also start in the cells of the lobules, which are the groups of glands that make milk [6-7]. This type of cancer is called lobular carcinoma. Both ductal carcinoma and lobular carcinoma can be in situ, which means that the cancer is still where it started and has not grown into surrounding tissues. They can also be invasive, which means they have grown into surrounding tissues [8]. Less common types of breast

cancer can also develop. These include inflammatory breast cancer, Paget disease of the breast and triple negative breast cancer. Rare types of breast cancer include non-Hodgkin lymphoma and soft tissue sarcoma [9]. Although China has a low incidence of breast cancer, the incidence of breast cancer has gradually increased, with studies indicating that the incidence among Chinese women will exceed 100 per 100,000 by 2022, and the total number of female breast cancer patients aged 35–49 years will reach 2.5 million by 2022. Therefore, studying the risk factors of breast cancer to reduce its incidence is of great significance [10]. Breast cancer is the most common cancer in women worldwide and is the leading cause of cancer death among women. In 2018, there were about 2.09 million newly confirmed breast cancer cases in women and about 630,000 deaths. The incidence of breast cancer varies worldwide, but is increasing. Although the incidence of breast cancer (36.1/105) and mortality (8.8/105) is relatively low worldwide, the incidence of breast cancer and mortality in Chinese women ranks first globally due to the large population in China, and has increased in recent years (17.6% and 15.6%, respectively). As the incidence of breast cancer continues to increase worldwide, so does disease burden, which has become a major global public health problem [11].

Breast cancer is a multifactorial disease that mainly includes genetic factors, environmental factors, and behavioural lifestyle factors. The aim of the present review was to explore the epidemiology and related risk factors of breast cancer worldwide to understand its prevalence and to help in early detection. The main risk factors for breast cancer are genetic factors, namely family history; diet and obesity, as the quality of life in our country improves, women are getting more and more obese, and their diet tends to be more and more high-fat; smoking and drinking; the other is ionizing radiation; still have namely menstruation, bear and whether lactation, these factors also can affect the occurrence of breast cancer; there is a great relationship between breast cancer and the change of estrogen inside the body. In life, we should avoid using cosmetics containing estrogen as far as possible to reduce the influence of exogenous hormones on the body. There's been a lot of controversy around these appeals. Therefore, it is necessary to systematically review the risk factors of breast cancer by using meta methods to guide clinical prevention and treatment [12].

Although Chinese scholars have conducted meta-analyses of breast cancer risk factors, in the present study, we conducted a meta-analysis of breast cancer risk factors in Chinese women by collecting relevant literature from 2001 to 2021 to provide basic data for the prevention of breast cancer in Chinese women [13]. A risk factor is something that increases the risk of developing cancer. It could be a behaviour, substance or condition. Most cancers are the result of many risk factors. But sometimes breast cancer develops in women who don't have any of the risk factors described below. Most breast cancers occur in women. The main reason women develop breast cancer is because their breast cells are exposed to the female hormones estrogen and progesterone. These hormones, especially estrogen, are linked with breast cancer and encourage the growth of some breast cancers. Breast cancer is more common in high-income, developed countries such as Canada, the United States and some European countries. The risk of developing breast cancer increases with age. Breast cancer mostly occurs in women between 50 and 69 years of age [14].

Breast cancer is a significant health concern worldwide and the most commonly diagnosed cancer among women. While the exact cause of breast cancer is not fully understood, researchers have identified several risk factors that can increase a woman's chances of developing the disease. Understanding these risk factors is crucial for early detection, prevention, and effective management of breast cancer [14]. Breast cancer is the most common cancer diagnosed in women, accounting for more than 1 in 10 new cancer diagnoses each year. It is the second most common cause of death from cancer among women in the world. Anatomically, the breast has milk-producing glands in front of the chest wall. They lie on the pectoralis major muscle, and there are ligaments support the breast and attach it to the chest wall. Fifteen to 20 lobes circularly arranged to form the breast. The fat that covers the lobes determines the breast size and shape. Each lobe is formed by lobules containing the glands responsible for milk production in response to hormone stimulation. Breast cancer always evolves silently. Most of the patients discover their disease during their routine screening. Others may present with an accidentally discovered breast lump, change of breast shape or size, or nipple discharge. However, mastalgia is not uncommon. Physical examination, imaging, especially mammography, and tissue biopsy must be done to diagnose breast cancer. The survival rate improves with early diagnosis. The tumour tends to spread lymphatically and haematologically, leading to distant metastasis and poor prognosis. This explains and emphasizes the importance of breast cancer screening programs [15].

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Risk factors for developing breast cancers among women

1. Personal history of breast cancer

Women who had breast cancer in the past have a higher risk of developing breast cancer again. The new breast cancer can develop in the same breast as the first cancer or in the other breast. Women who had ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) have a higher risk of developing a second breast cancer, but most women who had these cancers do not develop breast cancer again [16].

2. Family history of breast and other cancers

A family history of breast cancer means that one or more close blood relatives have or had breast cancer. Some families have more cases of breast cancer than would be expected by chance. Sometimes it is not clear whether the family's pattern of cancer is due to chance, shared lifestyle factors, genes passed from parents to children or a combination of these factors [17].

3. BRCA gene mutations

Genetic mutations are changes to a gene. Some gene changes can increase the risk of developing certain types of cancer. Inherited gene mutations are passed on from a parent to a child. Only a small number of breast cancers (about 5%–10%) are caused by an inherited gene mutation. BRCA1 (breast cancer gene 1) and BRCA2 (breast cancer gene 2) are normally found in the body. They are called tumour suppressor genes because they appear to play a role in controlling the growth of cancer cells. Mutations in the BRCA1 or BRCA2 genes can affect them so they no longer control cancer growth. These mutations are rare. They occur in about 1 in 500 people. Both men and women can inherit a mutated BRCA gene from either their mother or father. People who have the gene mutation can also pass it on to their children. If one parent has the mutation in 1 of the 2 copies of the BRCA gene, a child has a 50% chance of inheriting the gene mutation. This also means there is a 50% chance that a child will not inherit the gene mutation [18].

Studies show that women with inherited BRCA1 or BRCA2 gene mutations have up to an 85% chance of developing breast cancer in their lifetime. Women with these inherited mutations also have a higher risk of developing breast cancer at a younger age than other women. Women with a BRCA gene mutation also have a higher risk of developing cancer in both breasts. If they develop cancer in one breast, they have a greater risk of developing cancer in the other breast. Having BRCA gene mutations also increases a woman's risk of developing ovarian cancer at any age [19].

4. Dense breasts

Dense breasts have more connective tissue, glands and milk ducts than fatty tissue. Breast density is an inherited trait. Women with dense breast tissue have a higher risk of developing breast cancer than women with little or no dense breast tissue. Breast density can only be seen on a mammogram, but dense breasts also make a mammogram harder to read. On a mammogram, fatty tissue looks dark, while dense tissue looks white, like tumours, so it can hide a tumour [20].

5. Late menopause

Menopause occurs as the ovaries stop making hormones and the level of hormones (mainly estrogen and progesterone) in the body drops. This causes a woman to stop menstruating. If you enter menopause at a later age (after age 55), it means that your cells are exposed to estrogen and other hormones for a greater amount of time. This increases the risk for breast cancer. Likewise, menopause at a younger age decreases the length of time breast tissue is exposed to estrogen and other hormones. Early menopause is linked with a lower risk of breast cancer [21].

6. Late pregnancy or no pregnancies

Pregnancy interrupts the exposure of breast cells to circulating estrogen. It also lowers the total number of menstrual cycles a woman has in her lifetime. Women who have their first full-term pregnancy after the age of 30 have a slightly higher risk of breast cancer than women who have at least one full-term pregnancy at an earlier age. Becoming pregnant at an early age reduces breast cancer risk. The more children a woman has, the greater the protection against breast cancer. Not becoming pregnant at all increases the risk for breast cancer [22].

7. Hormone replacement therapy

The Women's Health Initiative (WHI) study showed the risk for breast cancer went up by about 1% for every year that women took estrogen alone and about 8% for every year that they took combined HRT. The study also found that the risk was increased even with comparatively short-term use of combined HRT compared to a placebo. The higher risk appears to disappear a few years after stopping HRT. The WHI study also showed that there was a significant drop in the rate of new cases of breast cancer from 2002 to 2004 among Canadian women aged 50–69 years. This drop coincided with a drop in combined HRT use. This trend was also seen in a number of other countries around the world, including the United States, Australia, Germany, the Netherlands, Switzerland and Norway. Researchers now believe that the risks of long-term use of combined HRT outweigh the benefits [23].

8. Being obese

Obesity increases the risk for breast cancer in post-menopausal women. Studies show that women who have never taken hormone replacement therapy and who have a body mass index (BMI) of 31.1 or higher have a 2.5 times greater risk of developing breast cancer than those with a BMI of 22.6 or lower. Ovarian hormones, estrogens in particular, play an important role in breast cancer. Many of the risk factors for breast cancer are believed to result from the overall dose of estrogen the breast tissue receives over time. The ovaries make most of the body's estrogen, but after menopause fat tissue produces a small amount of estrogen. Having more fat tissue can increase estrogen levels and so increase the chance that breast cancer will develop [24].

9. Estrogen

Both endogenous and exogenous estrogens are associated with the risk of breast cancer. The endogenous estrogen is usually produced by the ovary in premenopausal women and ovariectomy can reduce the risk of breast cancer. The main sources of exogenous estrogen are the oral contraceptives and the hormone replacement therapy (HRT). The oral contraceptives have been widely used since 1960s and the formulations have been upgraded to reduce side-effects. However, the OR is still higher than 1.5 for African American women and Iranian populations. Nevertheless, oral contraceptives do not increase the risk of breast cancer in women who stop to use them for more than 10 years. HRT involves the administration of exogenous estrogen or other hormones for the menopausal or postmenopausal women. A number of studies have shown that the use of HRT can increase the breast cancer risk. The Million Women Study in UK reported a relative risk (RR) of 1.66 between current users of HRT and those who never used it. A cohort study of 22,929 women in Asia demonstrated HRs of 1.48 and 1.95 after HRT use for 4 and 8 years, respectively. However, the risk of breast cancer has been shown to significantly decrease after two years of stopping HRT. The recurrence rate is also high among breast cancer survivors who take HRT, and the HR for a new breast tumor is 3.6. Since the adverse effects of HRT were published in 2003 based on the Women's Health Initiative randomized controlled trial, the incidence rate of breast cancer in America has decreased by approximately 7% due to the reduction in the use of HRT [25].

Pathogenesis of breast cancer among women

Breast tumours usually start from the ductal hyperproliferation, and then develop into benign tumours or even metastatic carcinomas after constantly stimulation by various carcinogenic factors. Tumour microenvironments such as the stromal influences or macrophages play vital roles in breast cancer initiation and progression. The mammary gland of rats could be induced to neoplasms when only the stroma was exposed to carcinogens, not the extracellular matrix or the epithelium. Macrophages can generate a mutagenic inflammatory microenvironment, which can promote angiogenesis and enable cancer cells to escape immune rejection. Different DNA methylation patterns have been observed between the normal and tumour-associated microenvironments, indicating that epigenetic modifications in the tumour microenvironment can promote the carcinogenesis. Recently, a new subclass of malignant cells within tumours called the cancer stem cells (CSCs) are observed and associated with tumour initiation, escape and recurrence. This small population of cells, which may develop from stem cells or progenitor cells in normal tissues, have self-renewal abilities and are resistant to conventional therapies such as chemotherapy and radiotherapy. Breast cancer stem cells (bCSCs) were first identified by Ai Hajj and even as few as 100 bCSCs could form new tumours in the immunocompromised mice. bCSCs are more likely to originate from luminal epithelial progenitors rather than from basal stem cells. Signalling pathways including Wnt, Notch, Hedgehog, p53, PI3K and HIF are involved in the self-renewal, proliferation and invasion of bCSCs. However, more studies are needed to understand bCSCs and to develop novel strategies to directly eliminate the bCSCs [19]. There're two hypothetical theories for breast cancer initiation and progression: the cancer stem cell theory and the stochastic theory. The cancer stem cell theory suggests that all tumour subtypes are derived from the same stem cells or transit-amplifying cells. Acquired genetic and epigenetic mutations in stem cells or progenitor cells will lead to different tumour phenotypes. The stochastic theory is that each tumour subtype is initiated from a single cell type. Random mutations can gradually accumulate in any breast cells, leading to their transformation into tumour cells when adequate mutations have accumulated. Although both theories are supported by plenty of data, neither can fully explain the origin of human breast cancer [26].

Biological prevention of breast cancer

Recently, biological prevention, mainly known as the monoclonal antibodies for the breast cancer, has been developed to improve the quality of life in breast cancer patients. One of the major targets of these monoclonal antibodies is HER2. About 20-30% of all breast cancer cases exhibit HER2 protein overexpression or *HER2* gene amplification. Trastuzumab (Herceptin), a recombinant humanized monoclonal antibody, is the first HER2-targeted drug to be approved by the FDA. It can directly interact with the C-terminal portion of domain IV in the extracellular part of HER2. Up to now, the anti-tumour mechanism of trastuzumab has not been clearly elucidated. Some potential mechanisms may be that trastuzumab can suppress the growth and proliferation of cancer cells by recruiting ubiquitin to internalize and degrade HER2, by activating the immune system against cancer cells via a mechanism called antibody-dependent cell-mediated cytotoxicity (ADCC) or

by inhibiting the MAPK and PI3K/Akt pathways. Trastuzumab was initially used for treating metastatic breast cancer (MBC) and found to be efficacious as a single agent with an objective response rate (ORR) of 26%. *In vitro* experiments have shown that trastuzumab has a synergistic effect with other anti-tumour drugs such as nimotuzumab, carboplatin, 4-hydroxycyclophosphamide, docetaxel and vinorelbine. The HERA and TRAIN trials demonstrated that chemotherapy combined with adjuvant trastuzumab for 1 year could improve the disease-free survival in patients with $HER2^+$ breast cancer (HR=0.76). A randomized phase II trial executed by Marty also showed that trastuzumab plus docetaxel was more efficacious than docetaxel alone in treating HER2-positive MBC, with the ORR of 50% versus 32%. However, side-effects such as congestive heart failure and left ventricular ejection fraction (LVEF) decline were found in trastuzumab-treated patients [4].

Diagnosis of breast cancer among women

1. mammography

Diagnostic mammography is an x-ray that uses small doses of radiation to make an image of the breast. It is used to follow up on abnormal results of a screening mammography or a clinical breast exam. Mammography can also be used to find an abnormal area during a biopsy [27].

2. Ultrasound

An ultrasound uses high-frequency sound waves to make images of parts of the body. It is used to find out if a breast lump is a solid tumour or a cyst. Doctors may also use ultrasound to guide them to the area to be tested during a biopsy. Women with advanced breast cancer may have an ultrasound to check if the cancer has spread to the liver [28].

3. Biopsy

A biopsy is the only definite way to diagnose breast cancer. During a biopsy, the doctor removes tissues or cells from the body so they can be tested in a lab. A report from the pathologist will confirm whether or not cancer cells are found in the sample. The type of biopsy done will depend on if the lump is palpable, which means that you can feel it, or non-palpable, which means you can't feel it. The doctor may use mammography or ultrasound to help them find the area to be tested. Most biopsies are done in a hospital, and you can go home when the biopsy is finished [29].

4. Core biopsy

Uses a special hollow needle to remove tissue from the body. Doctors use it to take a sample from a suspicious area in the breast. They may take several samples of the area during the procedure. Sometimes doctors use a special vacuum to remove more tissue through the hollow needle. This technique is called vacuum-assisted core biopsy [17].

5. Lymph node biopsy

A lymph node biopsy is a surgical procedure that removes lymph nodes so they can be examined under a microscope to find out if they contain cancer. Breast cancer cells can break away from the tumour and travel through the lymphatic system. The first place they may spread is the lymph nodes under the arm. Doctors use the number of lymph nodes that have cancer in them to help determine the stage of breast cancer [30].

6. Fine needle aspiration (FNA)

Uses a very thin needle and syringe to remove a small amount of tissue from a lump. Doctors use it to find out if the lump is a cyst or solid tumour. FNA cannot tell doctors if the cancer is non-invasive or invasive [31].

CONCLUSION

Breast cancer is the most frequently diagnosed cancer in women across 140 countries. Breast cancer is also influenced by genetic and environmental factors. Targeted prevention strategies against these risk factors should be taken ahead of time. Although the incidence rate of breast cancer is high in developed countries, the fact which we can't ignore is that almost half of the breast cancer cases and over half of deaths occur in developing countries. Breast cancer is a preventable disease, and there are adequate medical resources available in developed countries, which can protect against this disease, such as annual mammography screening or the daily use of chemopreventative drugs. These may be attributable for the higher survival rate of breast cancer patients in developed countries than that in middle-income or low-income countries.

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