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. In some developed countries, the 5-year relative survival rate of breast cancer patients is above 80% due to early prevention. In the recent decade, great progress has been made in the understanding of breast cancer as well as in the development of preventative methods. The pathogenesis and tumor drug-resistant mechanisms are revealed by discovering breast cancer stem cells, and many genes are found related to breast cancer. 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. These findings represent a small step in the long fight against breast cancer.

Keywords: breast cancer, pathogenesis, risk factor, prevention.

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Introduction

Breast cancer is one of the most common cancers in women worldwide, accounting for approximately 570,000 deaths in 2015. Over 1.5 million women (25% of all women with cancer) are diagnosed with breast cancer every year throughout the world 1,2. In America, it is estimated that 30% of all new cancer cases (252,710) among women are breast cancer in 2017 3. Breast cancer is a metastatic cancer and can commonly transfer to distant organs such as the bone, liver, lung and brain, which mainly accounts for its incurability. Early diagnosis of the disease can lead to a good prognosis and a high survival rate. In North American, the 5-year relative survival rate of breast cancer patients is above 80% due to the timely detection of this disease 4. Mammography is a widely used screening approach in the detecting of breast cancer and proved to help reduce the mortality effectively. Other screening methods, such as Magnetic Resonance Imaging (MRI), which is more sensitive than mammography, have also been implemented and studied during the last decade 5. There're numerous risk factors such as sex, aging, estrogen, family history, gene mutations and unhealthy lifestyle, which can increase the possibility of developing breast cancer 6. Most breast cancer occur in women and the number of cases is 100 times higher in women than that in men 3. Although the incidence rate of breast cancer in America increases year after year, the mortality rate decreases due to the widespread early screenings and advanced medical therapies. Biological therapies have been developed in recent years and proved to be beneficial for breast cancer. Here, we will focus on studies of the pathogenesis, related genes, risk factors and preventions of breast cancer over the past years.

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Pathogenesis

Breast tumors usually start from the ductal hyperproliferation, and then develop into benign tumors or even metastatic carcinomas after constantly stimulation by various carcinogenic factors. Tumor 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 7,8. Macrophages can generate a mutagenic inflammatory microenvironment, which can promote angiogenesis and enable cancer cells to escape immune rejection 9,10. Different DNA methylation patterns have been observed between the normal and tumor-associated microenvironments, indicating that epigenetic modifications in the tumor microenvironment can promote the carcinogenesis 11,12. Recently, a new subclass of malignant cells within tumors called the cancer stem cells (CSCs) are observed and associated with tumor 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 13-15. Breast cancer stem cells (bCSCs) were first identified by Ai Hajj and even as few as 100 bCSCs could form new tumors in the immunocompromised mice 16. bCSCs are more likely to originate from luminal epithelial progenitors rather than from basal stem cells 17. Signaling pathways including Wnt, Notch, Hedgehog, p53, PI3K and HIF are involved in the self-renewal, proliferation and invasion of bCSCs 18-21. However, more studies are needed to understand bCSCs and to develop novel strategies to directly eliminate the bCSCs.

There're two hypothetical theories for breast cancer initiation and progression: the cancer stem cell theory and the stochastic theory 11,22. The cancer stem cell theory suggests that all tumor subtypes are derived from the same stem cells or transit-amplifying cells (progenitor cells). Acquired genetic and epigenetic mutations in stem cells or progenitor cells will lead to different tumor phenotypes (Figure ​(Figure1A).1A). The stochastic theory is that each tumor subtype is initiated from a single cell type (stem cell, progenitor cell, or differentiated cell) (Figure ​(Figure1B).1B). Random mutations can gradually accumulate in any breast cells, leading to their transformation into tumor 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.