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BASIC ASPECTS OF THE ETIOLOGY AND PATHOGENESIS OF BREAST CANCER

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Abstract
Every year, October 15 is World Breast Cancer Day, the most common cancer among women. This day was established by the World Health Organization in 1993[1,2,3]. Let's consider how a tumor develops and how the mechanism of breast carcinoma formation can be triggered. Let us highlight the main risk factors for this disease.

Key words
pathogenesis of breast cancer, epidemiology of breast cancer, structure of the mammary gland, risk factors for breast carcinoma.

INTRODUCTION

Breast cancer or carcinoma is an oncological disease that is caused by the uncontrolled growth of epithelial cells in the mammary gland.

In 2022, breast cancer is the most common cancer among women in 157 of 185 countries. Breast cancer occurs in all countries of the world. Males account for approximately 0.5–1% of all breast cancer cases[4,5,6].

According to WHO, breast cancer ranked fourth in 2022 as the leading cause of death from malignant tumors, and this is greatly facilitated by the fact that most often breast cancer does not cause pain or discomfort until it spreads to nearby tissues.

According to WHO, in 2022, breast cancer was diagnosed in 2.3 million women and caused 670,000 deaths worldwide. Breast carcinoma occurs throughout the world in women of all ages after puberty, with incidence rates increasing with age.

The incidence of breast cancer is high in almost all developed countries except Japan, and low in Asia, Africa and South America. The highest incidence is observed among the white population of Australia, Hawaii, Switzerland, the USA, and among Jews in Israel[7,8,9]. However, among non-Jewish women living in Israel, the incidence is low. The incidence is low in China and Japan.

As for breast cancer mortality, the highest is observed in Denmark, the Netherlands, Great Britain, and Israel. The lowest mortality from breast cancer was recorded in China and Japan.

However, the incidence of breast cancer is increasing among migrants who move from countries with low incidence to countries with high incidence. For example, in the United States, the incidence of breast cancer is significantly higher among migrants of Japanese and Chinese descent than among Japanese and Chinese residents of their native countries.

In most countries of the world, the incidence of this disease is increasing. In China, the annual increase in incidence was 5%[10,11,12]. At the same time, breast cancer mortality began to decline in many Western countries.

Mammary glands are glands that produce milk. The glands are located on the chest on either side of the sternum. They lie on top of the ribs and pectoral muscles and are divided into three main parts:

- glandular tissue that produces milk and consists of 15-20 lobules. Inside each of them lie grape-like structures called alveoli, which are modified sweat glands surrounded by a basement membrane made mostly of collagen. If you enlarge the alveoli, you can see a layer of alveolar cells that secrete breast milk into the lumen of the alveoli. The alveoli are surrounded by special

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myoepithelial cells that contract and squeeze milk from the lumen of the alveoli into the milk ducts and out through the pores on the nipple.

- stroma – the second part of the mammary gland. The stroma surrounds the glandular tissue and contains adipose tissue, which makes up the majority of the breast. Supporting ligaments called Cooper's ligaments run through the stroma and help hold the breast in place[13]. These ligaments are attached at one end to the skin of the mammary gland and at the other to the pectoral muscles.

- under the skin above the mammary gland there is a network of tiny lymphatic vessels that collect lymph from the cells of the gland. Lymph from the lymphatic vessels drains mainly into five groups of lymph nodes in the axillary regions.

Glandular tissue cells contain receptors for certain hormones - estrogen and progesterone, which are produced by the ovaries, and prolactin, which is produced by the pituitary gland. These hormones stimulate alveolar cells to divide and increase in number, which increases the size of the lobules. Without these hormones, glandular cells cannot survive and undergo apoptosis. After menopause, estrogen production stops, causing alveolar cells to die, and over time the breast tissue is replaced by fatty tissue. During the menstrual cycle[14], the secretion of estrogen and progesterone increases, immediately after menstruation the secretion decreases, as a result, during the menstrual cycle, alveolar cells undergo division and apoptosis.

During cell division, there is a possibility that a genetic mutation will occur that can lead to the formation of a tumor. Therefore, as the number of menstrual cycles increases, the risk of tumor formation increases. Thus, early age at first menarche and late age at menopause are associated with an increased risk of developing breast tumors.

Likewise, medications containing estrogen may increase the risk of breast cancer. There is also evidence of a connection between the appearance of breast tumors and hyperestrogenemia.

The formation and metabolism of steroid sex hormones may depend on the type of diet, in particular, on the consumption of fat. Saturated fatty acids can inhibit the binding of estradiol by a special globulin protein that binds steroid sex hormones, which can lead to increased plasma concentrations of free estradiol[15,16,17]. A study of the influence of endogenous steroid sex hormones showed that in women with breast cancer, the concentration of total and free estradiol in the blood is higher than in healthy women of the same age. This difference is more pronounced for menopausal women. Some studies have found an association between the concentration or decrease in the binding capacity of SPGSH and the risk of breast cancer. Thus, at a high concentration and high ability of SPGSG to bind estradiol, the proportion of its free fraction decreases, which leads to a decrease in the risk of breast cancer.

Thus, it has not been reliably proven, but there may be a connection between eating high amounts of saturated fat and the risk of developing breast cancer.

The effect of the use of combined oral contraceptives on the risk of breast cancer still remains unclear.

Several epidemiological studies have found a statistically significant increase in the risk of developing breast cancer when using oral contraceptives in women over 45 years of age.

Also, a study conducted in England found an association between the risk of developing breast cancer and the use of oral contraceptives in women under 36 years of age[18,19,20]. The duration of COC use and the concentration of estrogen in them also had an effect. So the shorter the period of use and the lower the dose of estrogen, the lower the risk of breast tumors. Thus, it can be concluded that taking oral contraceptives most likely increases the risk of developing breast cancer.

However, about half of all cases of breast cancer occur in women who are not exposed to any specific risk factors other than gender and age[24].

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In cases where there is a family history of breast cancer, it is being studied to link its occurrence to specific mutations in tumor suppressor genes, such as BRCA 1, BRCA 2 and TP53, which slow down cell division or cause cells to die if they divide uncontrollably. BRCA 1, BRCA 2 mutations are autosomal dominant mutations that can be inherited and cause hereditary breast cancer; they also increase the risk of developing ovarian cancer.

Some breast cancers have mutations in the ERBB2 gene, which increases the number of human epidermal growth factor receptor two (HER-2), the activation of which promotes cell growth.

On the other hand, there are circumstances that are believed to reduce the risk of developing breast cancer - early pregnancy before age 25 and prolonged breastfeeding - which leads to a decrease in the concentration of estrogen in the blood.

Thus, with an increase in the number of pregnancies that result in childbirth, the risk of breast cancer continues to decrease. A woman who has given birth to three or more children has an approximately 65% lower risk than a woman who has not given birth.

Increased physical activity reduces the risk of developing cancer of this organ. One study of a cohort of American women showed that those who were actively involved in sports in their youth had a reduced risk of almost all hormone-dependent forms of cancer, namely breast cancer, ovarian and endometrial cancer.

More than 20 cohort and retrospective epidemiological studies have revealed a positive and statistically significant association between alcohol consumption and the risk of breast cancer. The risk of breast cancer has been shown to be higher in women who drink alcoholic beverages than in women who do not drink alcohol.

CONCLUSIONS

Thus, it becomes clear that an important cause of breast cancer is an increase in the concentration of estrogen or an increase in the number of menstrual cycles (which may be associated with the number of pregnancies and births, the duration of breastfeeding, and lifestyle characteristics)[21,22,23]. But there are forms of breast cancer that may be associated with inherited mutations in certain genes.

It is clear that there has been a long-term increase in the incidence of breast cancer. However, it may also be explained by increased screening among asymptomatic women and improved reporting of all breast cancer cases and deaths.

However, in most European and other countries, the increase in incidence and mortality from breast cancer is so significant that it is unlikely to be explained by screening or improved statistical work alone.

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