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Improving the Diagnosis and Drug Treatment of Patients with Metastatic Breast Cancer, Taking into Account Prognostic Factors

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ABSTRACT

Breast cancer is a malignant tumor characterized by rather aggressive growth and the ability to actively metastasize. This pathogenesis is due to the complex interaction of genetic, hormonal, metabolic, exogenous and other factors and is the most common malignant neoplasm among women in the world. Older age and being a woman are the strongest risk factors for developing breast cancer. Potentially modifiable factors associated with increased risk in women include weight gain after age 18 and/or being overweight or obese (in the case of postmenopausal breast cancer); menopausal hormone therapy (a combination of estrogen and progestin), formerly called hormone replacement therapy; alcohol consumption; and lack of physical activity. Breastfeeding for at least one year reduces the risk.

Breast cancer occupies a leading place in terms of incidence among other malignant tumors in the world and 5th in terms of the number of deaths. According to Global Cancer Observatory , in 2020, more than 2.26 million cases of breast cancer were registered worldwide , which is 11.7% of all cases of malignant neoplasms in both sexes. According to the standardized and "rough" indicators of the incidence of breast cancer, as well as in absolute terms, it is ahead of all malignant neoplasms. Thus, the standardized indicator in 2020 was 47.8 cases per 100 thousand people, and the “rough” indicator was 58.5 cases. The total number of deaths in 2020 reached 685.0 thousand people (6.9% of all deaths from cancer). In terms of absolute mortality rates (both sexes), breast cancer is inferior to cancer of the lungs, colon, rectum and anus , liver and stomach and ranks 5th in the ranking, but in terms of standardized and “rough” values it is already in 2nd place (13.6 and 17.7 cases per 100 thousand people, respectively).[50].

A family history of breast cancer increases the risk of its development, but most patients diagnosed with breast cancer do not have a family history of cases of this disease in close relatives. Certain inherited highly penetrant mutations in genes significantly increase the risk of developing breast cancer, with mutations in the *BRCA1* , *BRCA2* , and *PALB-2* genes being dominant .[50]

The incidence rate of BC is steadily increasing. The main carcinogenic factor is the effect of estrogens on the epithelium of the gland ducts [17]. In 2022, approximately 287,850 women and 2,710 men will be diagnosed with invasive breast cancer for the first time in the US, with an additional 51,400 cases of ductal carcinoma diagnosed in women in situ (DCIS). It is estimated that 43,780 deaths from breast cancer will occur in 2022 (43,250 in women, 530 in men). [18] Since the mid-2000s, rates of invasive breast cancer in women have increased by about 0.5% per year. The death rate from breast cancer among women peaked in 1989 and has since decreased

by 42% as of 2019, mainly due to earlier detection through screening, as well as increased awareness of breast cancer and improving treatment. This decline means about 431,800 fewer breast cancer deaths over this time period than would be expected in the absence of this progress. However, the mortality rate for black women remains 41% higher than for white women despite lower incidence. [18].

Concerning the role of the hereditary factor in the development of breast cancer, it is necessary to note its role in about 5-10% of diseases. The hereditary form of cancer is more often diagnosed in young women of reproductive age [18]. As clinical observations show, the presence in the family of relatives with breast cancer significantly increases the risk of developing the disease. In this regard, a special nosological form of pathology was identified - breast cancer, within which the presence of various genetically determined forms is possible. Moreover, the authors do not exclude the possibility of the presence in the population of two forms of breast cancer - hereditary and sporadic.

Risk factors.

The main risk factors for developing breast cancer are as follows:

- hereditary predisposition;
- shifts in the hormonal balance, in particular, violations of the production and reception of gonadotropic hormones of the pituitary gland, as well as estrogens, progesterone, thyroid hormones, prolactin - the main regulators of the proliferation and differentiation of the epithelium of the ducts and alveoli of the mammary gland and their functions;
- age factor (in 85% cancer develops after 40 years);
- development of immunodeficiency and impaired elimination of tumor cells;
- the presence of feminizing ovarian tumors, accompanied by hyperestrogenism ;
- the use of estrogen replacement therapy to eliminate the symptoms of menopausal and post-castration syndromes;
- the presence of hyperplastic processes in the mammary gland: fibroadenomatosis and fibroadenoma, intraductal papilloma;
- risk factors for the development of breast cancer include such forms of extragenital pathology as obesity, diabetes mellitus, hypertension, as well as chronic exposure to stress stimuli;
- the risk of developing breast cancer increases with a history and previous treatment of ovarian, endometrial, colon cancer;
- a real modifying effect on the body and the frequency of occurrence in the population of hormone-dependent neoplasms is exerted by the nature of nutrition, excess fat and polyunsaturated fatty acids in food;
- breast risk factors include the first birth after 34 years, abortion after 35 years, menopause after 50 years and others.

Based on the study of individual pedigrees, the following criteria have been proposed for the selection of "hereditary" breast cancer:

earlier age of onset of the disease;

bilateral lesion;

"vertical" transmission of the disease;

the presence of specific tumor associations;

improved patient survival.

A number of researchers express the point of view that one of the key risk factors for developing breast cancer is increased production of insulin- like growth factor I (IGF). The IPFR receptor is considered essential for cell division, and its increased expression leads to neoplastic transformation of cells [9]. The point of view is expressed that, along with IPFR, insulin plays an important role in the regulation of mitogenic activity of cells, facilitates the development of the stage of tumor growth promotion. In this regard, there are indications of the role of hyperinsulinemia as a risk factor in the development of a number of tumors.

Reproductive and hormonal factors that increase risk include a long menstrual history (menstrual periods that start early and/or end late in life); not have children or have children over 30; high natural levels of estrogen or testosterone; and recent use of hormonal contraceptives.

It has been established that the process of promotion in breast cancer, as well as neoplasia of other localizations, is associated with a powerful induction of the estrogen receptor system. Estrogen-induced growth factor proteins have autocrine or paracrine effects. It has been established that polypeptide growth factor receptors belong to the ERBB family and are expressed on cell membranes, with ERBB2 or HER2/ neu being the most important. In the process of intense hormonal stimulation of estrogen receptors in the mammary gland, an increase in the formation of transforming growth factor alpha (TGF-a), belonging to the EGF (epidermal growth factor) family, occurs. TGF- a - stimulates mitotic activity, growth of tumor and normal cells of epithelial origin, and has angiogenic activity [9, 32, 35, 38]. At the same time, the formation of the estrogen-receptor complex induces the synthesis of insulin-like growth factor and inhibits the formation of transforming growth factor beta (TGF-|3). The latter belongs to the EGF family, inhibits the division of tumor and normal cells, and increases their differentiation [9, 36, 37, 40].

An important role in the mechanisms of breast cancer induction is given to an increase in the content of free estradiol in the blood, which is most pronounced in menopausal women. Oral contraceptives and hormonal drugs used during menopause as replacement therapy can serve as a source of carcinogenic promotion of mammary gland epithelial cells .

One of the leading risk factors for developing breast cancer is hereditary or acquired hypothyroidism. As it turned out, the conversion of estradiol fractions of estrogens into estriol depends on the level of thyroid hormones . Moreover, under conditions of hypothyroidism, this conversion of hormones is intensified [6, 9]. It has also been shown that with a decrease in the optimal level of thyroid hormones, stimulation of the growth of epithelial cells of the mammary glands, the development of dysplasia and neoplasia, occurs.

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