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EPIDEMIOLOGY OF EDEMATOUS AND NODULAR FORMS OF BREAST CANCER

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Abstract: The article discusses the epidemiology of breast cancer. The features of morbidity and the significance of constitutional factors – age, menstrual status, height, weight, body mass index-were studied.

Key words: breast cancer; edematous, nodular forms of breast cancer; body mass index, age, menstrual status

Introduction

РакBreast cancer (BC) is one of the most important problems of oncology due to the steady increase in its incidence in all countries of the world. In the United States and Western Europe, 25-30% of all new cancer cases in women and 18-20% of all cancer deaths in women are caused by breast cancer. The average ageof patients diagnosed with breast cancer for the first time in 2021 was 60.5 years. The estimated incidenceof breast cancer over 10 years (from 2011 to 2021) increased from 57.42 to 71.22 per 100 thousand population, that is, by 24.78%, the average annual growth rate during this period reached 2.24%.

Thelifetime risk of developing breast cancer ranks firstamong all nosologies – 4.96% (2021). Breast cancer is a heterogeneous disease, the pathogenesis of which is due to the complex interaction of genetic, hormonal, metabolic, exogenous and other factors. Breast cancer is most common in Europe (180 thousand cases per year) and North America (USA – more than 130 thousand cases per year). The largest increase in breast cancer cases is observed in Canada, the United States, Sweden, Spain, and Finland. The highest incidence – 80-90 per 100 thousand

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women – in Hawaii, British Columbia and California, in Japan – the lowest – 12-15 per 100 thousand women. In Eastern Europe, the incidence rate is 40-60 per 100 thousand women, in India, Africa and China, this figure is lower than in the Americas, but higher than in Europe.

Extremely rarely, the disease occurs in young women under 20 years of age, rarely-before 30 years, but then the incidence curve depending on age rises sharply, decreasing in deep menopause after 70 years [8]. The morbidity rate among women of different social strata is not uniform. The greatest risk of developing breast cancer is among women of high social status. About 66% of women with breast cancer are unaware of the existence of risk factors for the disease. Currently, in clinical practice, there are two main forms of breast cancer – nodular and edematous. The nodular form of cancer is about 75% and is represented by all stages. Edematous forms (infiltrative-edematous, edematous) of breast cancer (ORC) account for about 15% and belong to special forms characterized by an unfavorable prognosis and an extremely aggressive course with rapid locoregional and distant metastasis; the main clinical sign of these forms is the presence of breast edema [11]. This sign alone is sufficient to establish stage IIIB or IV (in the presence of distant metastases), regardless of other factors – the size of the tumor, the presence and number of metastatic lymph nodes, etc. The pathogenesis of edema is not fully understood. Most researchers believe that the development of breast edema is associated with the biological properties of the tumor, high rates of doubling, and its production of vasoactive and other factors that retain fluid inthe breast[14]. Taking into account the interrelation of the "tumor – organism" system in the development of edema, we can also talk about hormonal predictors of edema development and, consequently, about possible constitutional features of patients with infiltrative edematous cancer. An indirect confirmation of the above is the data of some authors on a significant decrease in edema when using prolactin -blocking drugs (perlodel, etc.) and switching off ovarian function, regardless of the level of tumor hormone receptors [5]. The question of the constitutional features of infiltrative-edematous breast cancer is poorly studied and insufficiently presented in the literature. The aim of the study was to determine the influence of certain constitutional factors on the development of certain forms of breast cancer; to study the features of growth, body mass index, and menstrual status in patients with nodular and diffuse forms of breast cancer.

The analysis of literature sources allowed us to present the features of breast cancer morbidity in the following way and show the significance of constitutional factors: I. Gender. The ratio of affected women to men is 135:1. II. Age. The highest risk of developing breast cancer is in the age group of 55-65 years and about 10% are younger than 30years. According to A. A. Dorofeev (2013), in infiltrative edematous cancer, compared with nodular forms, there is a smooth increase in the incidence from 40 to 55 years and at a later stage of menopause [5]. III. Anthropometric data. There is a link between anthropometric data and breast cancer risk. According to P. A. Van den Brandt (2000), height is an independent risk factor for

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postmenopausal breast cancer, whereas in pre-menopausal women, this relationship is less clear. The EPIC research program with the participation of nine European countries studied data on 73,542 women before menopause and 103,355 after menopause, and calculated indicators of the relative risk of breast cancer depending on height, weight, BMI, waist and hip circumference [16]. IV. Menstrual status. With the early onset of menarche (up to 13 years), the risk increases 2-2.5 times; it also increases with late menopause (after 55 years). Women with artificial menopause after bilateral ovariectomy before the age of 45 have half the risk compared to those with natural menopause at 55 years and older. Reducing the risk of breast cancer in early menopause is associated with a decrease in the proliferation of gland cells in the absence of menstrual cycles and with a decrease in estrogen activity during this period. V. State of the reproductive system. Back in 1961, it was shown that nulliparous women have a higher risk of developing breast cancer, while those who gave birth and had a pregnancy before the age of 25 are protected from this disease. The risk increases by 40% in women who have had their first pregnancy and delivery after the age of 30, as well as if they have a history of abortions, especially before the first birth. Subsequent pregnancies help reduce the risk of developing a tumor. Many authors believe that the risk of the disease is increased not only in unmarried women, but also in those who are married late, with irregular sex life, low libido, frigidity, protection from pregnancy, the presence of complicated abortions in the anamnesis, polygamy, extramarital sexual contacts. Impaired ovarian function, hyperplastic processes increase the risk of breast cancer. Lactation may reduce the risk of breast cancer. Breast-feeding for 12 months reduces the risk of breast cancer by 4.3%. VI. Hormonal factors. The main direction in the search for the causes of breast cancer development at present is the study of molecular and biological processes that cause uncontrolled invasive growth and metastasis of the tumor with the development of its hormone resistance. In the complex of causes, estrogens play a significant and possibly decisive role [11]. An increase in the concentration of estrogens increases the proliferative activity of liver tissue cells тканей-мишеней(breast, uterus, etc.), leading to an increased risk of developing malignant neoplasms in them. Two main types of hormonal carcinogenesis can be distinguished: promoter carcinogenesis, in which conditions for increasing the number of tumor cells are created under the influence of hormones, and genotoxic carcinogenesis [2]. The two main estrogenic fractions – estradiol and estrone – are formed under the influence of the aromatase enzyme from the androgenic precursors of testosterone and androstenediol. Interconversions of estradiol and estrone are carried out with the participation of the enzyme 17b hydroxy steroidгидрокси dehydrogenase [21]. A number of researchers believe that the metabolites that occur during interstitial formation of hydroxy derivatives of estrogens have carcinogenic and genotoxic effects [28]. It has also been established that the so-called catecholestrogens, i.e. metabolites of estrogens formed as a result of the introduction of a hydroxyl group into the 2nd or 4th position of the molecule, play an important role in hormonal carcinogenesis [15]. One of the important variants of the effect of

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estrogens on the cellular apparatus may be associated with the inhibition of DNA repair. L. M. Berstein (2000) found that under the influence of certain agents (radiation, smoking, alcohol, excessive consumption of saturated solid fats), a phase change in the effect of estrogens develops in the form of a weakening of their hormonal component

(induction of progesterone receptors) and an increase in the degree of DNA damage [2]. Estrogens found in the circulatory system enter it from various sources, the most important of which in women of reproductive age are the ovaries. The biosynthesis of estrogens in menopause is performed extrahonadally, in particular in adipose, muscle tissues, and the central nervous system. In the gonads and extra-gonadally, estrogens are formed from androgen precursors, based on the same biochemical reactions under the action of the aromatase enzyme. Peripheral aromatization of androgens in adipose tissue in overweight and obese postmenopausal women, resulting in an increased concentration of circulating estrogens, is one of the reasons for the association between postmenopausal obesity and breast cancer. The use of oestrogen-based hormones during pregnancy increases the risk of breast cancer. The exogenous effects of hormones include hormone replacement therapy (HRT) during peri-and postmenopausal periods, as well as the use of oral contraceptives. HRT with estrogens or combined estrogens is effective in reducing the severity of menopausal symptoms. The use of hormone replacement therapy in the postmenopausal period is a controversial risk factor: HRT slightly (2.1 times) increases the risk of developing breast cancer only during its use, after the end of HRT, this risk decreases. It has been found that after stopping HRT, the risk of breast cancer decreases, and then completely disappears within five years. The increased risk with combined medications (estrogens + progestins) is greater than with estrogen alone. The duration of HRT (oral contraceptives) with minimal risk is two years. There is evidence of an increased risk of breast cancer when starting taking combined oral contraceptives at a young age-up to 20 years. A slight increase in the percentage of women with breast cancer is observed with continuous use of oral contraceptives for more than 10 years. VII. Mastopathy and precancerous diseases of the breast. Mastopathy is a dishormonal disorder. hyperplastic process in the mammary gland, characterized by a wide range of proliferative and regressive tissue changes with an abnormal ratio of epithelial and connective tissue components. If the proliferative activity of the disease is low, the risk is minimal. It increases by more than three times with atypical epithelial proliferation. Ductal and lobular carcinomas in in situ increase the risk of invasive breast cancer by 8-10 times. It was found that the risk of breast cancer increases in individuals who underwent a breast biopsy for benign diseases.

Concomitant oncological diseases. The risk of developing breast cancer is twice as high in patients with endometrial or ovarian carcinoma. IX. Ionizing radiation. An exposure dose of 100 rad increases the risk of breast cancer by three times. Given the sensitivity of the breast to radiation at a young age, mammographic screening is recommended after the age of 35. X. Alcohol consumption. Daily consumption of 50 ml of alcohol increases the risk of breast cancer

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by 1.4-1.7 times, which is due to an increase in the activity of estrogens in the blood serum. XI. Genetic factor. It was found that the average age of hereditary cancer is 44 years, which is approximately 10-16 years earlier than in the population. Hereditary breast cancer can be combined with other types of tumors. The BRCA1 and BRCA genes have been identified as a genetic substrate of breast cancer2. BRCA1 is a cytosomal dominant gene located on chromosome 17. Its expression increases the overall risk of breast cancer by up to 85%. BRCA2 is located on chromosome 13. Expression of this gene usually increases the risk of developing highly differentiated breast cancer. Endocrine and metabolic factors associated with concomitant and previous diseases are potential risk factors: a) obesity; b) hypertension; c) diabetes mellitus of the elderly; d) atherosclerosis; e) liver diseases; f) hypothyroidism; g) dyshormonal hyperplasia of the mammary glands.

Obesity – the accumulation of fat in the body, leading to an increase in excess body weight by 20% or more from the average normal values, is characterized by excessive fat deposition in the body's fat depots and is not only a medical, but also a social problem. In industrialized countries, individuals suffering from various forms of obesity make up 20 to 30% of the total population, and 40 to 50% are overweight. Currently, the most widespread is the so-called body mass index (BMI), which best correlates with the mass of adipose tissue in the body (Gerrow D., 1981). In postmenopausal women, the use of hormone replacement therapy (HRT) affects the relationship between body size and breast cancer development. In women who do not use HRT and suffer from

If you are obese (BMI greater than 30), the risk of breast cancer is 31% higher than in women with a BMI less than 25. An increased risk of breast cancer among HRT users is found in thin women. In postmenopausal women who do not take exogenous hormones, overall obesity is a significant prognostic factor for breast cancer, while excess abdominal fat (the ratio of waist circumference to hip circumference) is not associated with breast cancer. Among women after menopause, there are unreliable positive associations of breast cancer with weight and BMI [13, 24]. S. Chang, A. U. Buzdar, and S. D. Hursting noted a higher BMI (26.65 kg / m2) in 68 women with infiltrative edematous cancer compared to 143 patients with non-edematous cancer of 22.27 kg / m2). The average weight was 77.6 and 68 kg, respectively [20]. All factors in the pathogenesis of obesity play a direct or indirect role in the development of hyperestrogenemia – one of the most significant risk factors for breast cancer. XIII. Previous breast cancer. Women treated for breast cancer have a 0.5 – 1% higher risk of developing breast cancer with each subsequent year of life. XIV. Geographical factors and nutrition. The incidence of breast cancer in the world varies depending on geographical factors and the socio-economic level of development of the country. There is a difference between the incidence in the United States, Western Europe and South America.East Asia. In the United States, the incidence is five times higher than in Japan. Differences may be related to environmental factors, lifestyle, and dietary patterns. Asian

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people eat a lot of rice, seafood, vegetables, fruits, green tea, and the diet of residents of Western European countries is characterized by the use of large amounts of meat and fat. The consequence of a high-calorie diet with a high fat content is overweight and obesity. In obesity, excess estrogen is deposited in adipose tissue, leading to hyperestrogenism and an increased risk of breast cancer. In areas with high morbidity rates, women start sexual activity later, have more frequent abortions, have fewer pregnancies, childbirth and lactation, and have a large number of unmarried women in these areas. Thus, in theseregions, factors that disrupt the physiological function of the genitals and mammary glands in women prevail. The constitutional features of breast cancer patients were studied at the P. A. Herzen Moscow Institute of Medical Research, and the influence of overweight and obesity in women of various age categories on the development of a certain form of breast cancer was analyzed. Comparison of the two main forms of breast cancer (edematous and nodular) by some criteriaлее a large group of breast cancer patients, and its share in edematous breast cancer is almost half and significantly higher than in the nodular form. This age group belongs to the category of increased risk of breast cancer, where the period of perimenopause prevails. This fact indirectly confirms the opinion about the importance of the hormone factor in the pathogenesis of edematous cancer. The average age of patients with edematous cancer is slightly lower than that of nodular cancer – 53 and 56.2 years, respectively (P < 0.005) (Fig. All patients in our study had their height and weight measured at admission to calculate their body mass index. There were no differences in height, the average height was 162.36 cm for edematous cancer and 162.2 cm for nodular cancer. There was a significant difference in weight (Table 1). The distribution of patients with edematous and nodular forms of breast cancer depending on body mass index is shown in Figure 2 and Table 2. It is noteworthy that the majority of patients in both groups are overweight.

Their study groups. Moreover, a statistically significant higher indicator of excess weight was determined in patients with the most prognostically unfavorable form of cancer – infiltrative edematous.

Conclusions 1. In the epidemiology of breast cancer, constitutional factors are essential. 2. The body mass index of breast cancer patients is significantly higher than the average values in the healthy population. The development of edematous breast cancer is more likely in overweight and obese patients, while the risk of developing nodular breast cancer is high in both normal and overweight patients. 3. Edematous cancer is more likely to occur during perimenopause. 4. The average age of patients with edematous cancer is slightly lower compared to nodular cancer-53 and 56.2 years, respectively.

Table 2. Sample of breast cancer patients by BMI characteristics

BMI Minimum BMI Maximum BMI Average BMI n

Edematous forms 18,57 62,07 29,2 300

Nodal forms 16.4 44.1 27.7 366

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