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CLINICAL ANALYSIS OF RISK FACTORS FOR BREAST CANCER IN YOUNG WOMEN

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Abstract
Breast cancer in young women is more often aggressive but less common than in older women. Characteristic features include more aggressive tumor types, difficult diagnosis due to high breast tissue density, and frequent detection of the disease at late stages. Risk factors include genetic predisposition, early onset of menstruation, late first birth, and lack of breastfeeding.

Keywords: Cancer, breast cancer, cancer in young women.

Introduction

Globally, just under 7% of breast cancers are diagnosed in women under the age of 40. Women who have:

- personal history of breast cancer or certain other breast diseases,
- cases of breast cancer in the family, especially in a mother, daughter or sister,
- history of radiation therapy to the chest area before the age of 40 years,
- genetic defect, such as mutation of the BRCA1, BRCA2, CHEK2 and other genes,
- the beginning of menstruation before the age of 12.

For some women, the age of birth of the first child matters. Other risk factors include high breast density, alcohol abuse, obesity, and race. According to some studies, taking contraceptives can also increase the risk of developing breast cancer. [5,9].

According to the literature, breast cancer occurs in 23% of patients in the reproductive period, mainly in women with nodular mastopathy [3, 4]. The mammary glands as part of the female reproductive system are an anatomically and functionally complex organ that undergoes pronounced cyclic changes over decades [1, 3]. In recent decades, there has been a steady increase in the incidence of benign breast dysplasia (VMD), which is diagnosed in 60–80% of women of reproductive age [5]. Of the total number of patients with diseases of the reproductive system, almost two-thirds go to the doctor with complaints of breast diseases. In most of them, at the first examination and clinical examination, certain deviations from the norm are revealed. Along with this, in 10–20% of cases, during the medical examination of women who do not complain, instrumental examination reveals pathological changes that require further observation [3].

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However, in the reproductive period, the diagnosis of breast cancer is difficult due to the variety of manifestations of clinical, radiological and pathomorphological forms of malignant neoplasms of the mammary gland.

Although the basics of chemotherapy are the same for patients of all ages, young women have some peculiarities. Before starting systemic treatment, it is important to consider options for preserving fertility, egg retrieval and the need to consult a fertility specialist in case of planning a pregnancy in the future are always discussed with patients. It is also important to be able to perform genetic testing to assess the presence of mutations, as its results can affect the choice of therapy. [6,10]

Objective: Clinical assessment of risk factors for breast cancer in women of early reproductive age with benign breast dysplasia.

Materials and methods

The analysis of medical records of 105 women aged 14 to 30 years (average age 25.5 years) with VDM, who in 2015–2020 were at the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology of the Surkhandara branch, observation in the outpatient department, applied there for consultative assistance.

The study participants were divided into three groups: group I – 49 (46.6%) patients with diffuse fibrocystic mastopathy (DPKM), group II – 29 (27.6%) women with nodular mastopathy, group III (comparisons) – 27 (25.7%) women with diffuse cystic changes in the mammary glands. During the 3 years of annual follow-up and ultrasound of the mammary glands, the participants of the III group did not have a negative structural transformation of the mammary glands, and therefore they were presented by us as a comparison group.

All patients underwent a general clinical examination (study of complaints, medical history, family anamnesis), palpation of the mammary glands and areas of regional metastasis, laboratory study (determination of the presence or absence of *the BRCA1* and *BRCA2 genes* on the basis of family history), ultrasound of the mammary glands. X-ray mammography (RMG), as well as morphological examination of biopsy material, were performed in the first two groups according to indications.

The technique of ultrasound of the mammary glands consisted in obtaining sequential sections of the mammary gland in four quadrants on the Medison-530 device (China) using a linear transducer with a frequency of 5 MHz. The localization of pathological processes, the condition, number and nature of the distribution of the stroma, glandular structures, milk ducts and adipose tissue were assessed. The clarity of differentiation of mammary gland tissues, the presence of disorders in the architectonics of the mammary glands with their assignment to the group of diffuse or focal forms of mastopathy were taken into account.

All changes found in one breast were compared with symmetrical sites in the contralateral breast. At the second stage, the sensor was returned to the area of atypical tissue structure. At the same time, the condition of the contours, visualization of the front and back walls, and the presence of additional acoustic effects were determined.

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According to the standards, mammography is performed on women 50 years and older (once every two years), as well as on women 35-40 years old, if there is a family history of breast cancer or a mutation of the *BRCA1* and *BRCA2 genes*.

If a malignant tumor is suspected, the study is carried out at any age. Mammography was performed in two projections: craniocaudal and oblique. The latter displays the tissue of the organ in the largest volume and is performed at an angle of 45 degrees for simultaneous visualization of the axillary process and lymph nodes. The study was performed on both sides, regardless of the location of the suspicious focus, in order to timely diagnose clinically asymptomatic cancer in the opposite mammary gland.

When analyzing mammograms, the characteristics of the tumor (localization, size, density, contours, the presence of microcalcification), the relationship with the surrounding tissues, the state of the skin, subcutaneous tissue, gland tissue, the presence of multifocality or multicentricity, and the characteristics of regional lymph nodes were assessed.

If tumor formations were detected, fine-needle aspiration biopsy or core biopsy was performed, followed by cytological and histological examination of the obtained material with determination of receptor status.

Processing of digital data and graphical display of the results were carried out using the standard Microsoft Excel application package.

Outcomes

The results of the examination in three groups showed that among dyshormonal diseases of the mammary glands, DPKM prevailed over the nodular form of mastopathy (46.6% and 27.6%, respectively). The study found that DPKM occurs in women of early reproductive age from the age of 16, and after the age of 25, its frequency reaches 55%.

Nodular mastopathy has been diagnosed predominantly in women over 24 to 26 years of age, and the incidence of this form of VDM remains stable until the age of 30 in this study.

During examination and palpation of the mammary glands in patients with diffuse and nodular VDM, a distinctive feature of the latter was tenderness (local or diffuse), depending on the phase of the menstrual cycle with its regular nature. At the same time, the number of women with nipple discharge was higher in the group with a predominance of the nodular component — 23% versus 17% of patients with DPKM.

Since benign diseases and breast cancer have common etiological factors and pathogenetic mechanisms, many risk factors for the development of mastopathy and breast cancer are identical. The analysis of the results showed that patients of both groups, regardless of the form of mastopathy, had a burdened heredity for oncological diseases in every third case. Their relatives often had malignant neoplasms of the female reproductive system. In women with nodular mastopathy, every fifth relative of the first degree of kinship had a malignant tumor of the mammary glands.

The analysis of the obstetric and gynecological history showed that in women with DPKM, menarche was 16 months earlier than in the nodular VDM group and the comparison group, and its age was on average 11 ± 1.2 years. However, the length of the menstrual cycle varied widely, from 31 to 52 days (about 36 days on average).

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Impairment of fertility function in women of the study groups was not noted. All patients had a history of pregnancies, which ended in childbirth in 60% of them. The incidence of VBM was 1.5 times higher in women with a history of two or more induced abortions. In patients with nodular mastopathy, an increase in the number of spontaneous miscarriages in early pregnancy (up to 25%) was revealed.

Early cessation of lactation (at 1–4 months) due to hypogalactia and refusal of the child to breastfeed was characteristic of every second woman, regardless of the form of VDM, as well as for women in the comparison group. Only about 19 (22.1%) of the 86 participants had breastfed for more than 1 year. According to the literature, the duration of lactation of 1 year or less often is associated with breast pathology than the duration of less than 6 months [4, 7].

There are no clear recommendations in the literature regarding hormonal therapy in patients with VDM and assessing its effectiveness.

Women of reproductive age inevitably face the question of using hormonal drugs to correct menstrual and reproductive function, as well as for the purpose of contraception. Numerous randomized trials have proven that taking hormonal contraceptives does not increase the risk of developing breast cancer [8]. However, the effect of various hormonal agents on the course of VMJ has not been studied enough [1, 8].

We noted that before contacting mammologists, every third woman with DPCM used hormonal contraception from 6 to 22 months, and only 15% of patients with nodular VDM occasionally used hormonal contraceptives. This is likely due to the fact that they had a regular menstrual cycle, which determined their choice in favor of barrier methods of contraception. Thus, it is impossible to conclude about the benefits or harms of hormonal contraceptives.

It is known that some somatic diseases are considered as risk factors for dyshormonal diseases and are pathogenetic stages in the development of the latter.

In the structure of extragenital diseases in women of group I, gastrointestinal diseases prevailed (n = 17; 40.5%), chronic bronchitis of a smoker was present in 13 (31.0%), and impaired fat metabolism in 9 (21.4%). Participants in group II had metabolic-neuroendocrine disorders, which were definitely associated with pregnancy and childbirth. Among them, fat metabolism disorders and gestational diabetes (n = 7; 33.3%) and thyroid pathology (n = 5; 23.8%) should be noted. Thus, in patients with nodular mastopathy, a predominantly hypothyroid state was revealed.

The results obtained are consistent with the literature data on the role of thyroid dysfunction in the etiopathogenesis of VDM. It is thyroid diseases, mainly hypothyroidism, that contribute to the development or progression of pathological changes in the mammary glands. Reduced thyroid function increases the risk of VDM by more than 3.8 times. Thyroid hormones act on the mammary gland directly or through the effect on the receptors of other hormones, in particular prolactin.

Thus, an increase in the secretion of thyrotropin-releasing hormone stimulates the production of not only thyroid-stimulating hormone, but also prolactin. Prolactin is able to increase the content of estradiol receptors in the breast tissue, as well as to have a direct stimulating effect on proliferative processes in the peripheral organs of the reproductive system, which is realized by increasing the synthesis of estrogens in the ovaries. Deviation from the physiological norm of the secretion of thyroid hormones, which are modulators of the action of estrogens at the cellular level, contributes to the progression and formation of hyperplastic processes. Under their influence, the level of

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epidermal growth factor receptors in the mammary gland is regulated, which stimulates the proliferation of epithelial cells and inhibits their functional differentiation.

The study showed a relatively high percentage of patients with inflammatory diseases of the genital organs in groups I and II (19 (45.2%) and 11 (52.4%), respectively). Endometriosis and small uterine fibroids were more often observed in patients with nodular mastopathy: 33.3% versus 26.2% in the DPCM group and 23.8% versus 16.7%, respectively.

Echographic examination revealed ductoids in 4 (4.6%) participants. In patients of group I, fibrocystic changes in the mammary gland were visualized, in group II — echographic signs of focal fibrosis of breast tissue, group III — diffuse cystic changes. The diagnostic value of the ultrasound method for benign pathology is the same as for mammography. The advantages of the method include the absence of radiation exposure, the ability to obtain an image of X-ray negative formations, exclude damage to the supra- and subclavian lymph nodes, and detect retromammary formations. At the same time, it should be noted that the method has a weak resolution in the detection of small tumors in dense glands with a small amount of adipose tissue and in the differential diagnosis of nodular forms of mastopathy and cancer.

The study of benign diseases of the mammary glands showed that the risk of developing breast cancer depends on the degree of proliferation and atypia of cells. There was a 2-fold increase in the risk of breast cancer in patients with atypical hyperplasia and burdened heredity compared to patients with an unburdened family history and cell atypia. A number of authors believe that mastopathy with epithelial proliferation increases the risk of breast cancer by 2–3 times, mastopathy with moderate cell atypia — by 20–40 times [2].

At present, puncture with cytological examination of the material occupies an important place in the diagnosis of breast cancer. This method can be used to diagnose cancer in 89.4–97.3% of patients [3, 6]. All women with nodular mastopathy underwent an ultrasound-guided puncture, and 67% of them were found to have atypical cells.

In Group I, aspiration biopsy was positive for atypical cells in 12 (28.6%) patients, and in Group II — in 9 (42.9%) patients. These patients underwent RMG, as a result of which it was established that in the diffuse form of mastopathy, breast cancer occurred in almost every fifth patient (n = 10; 23.8%), and in the nodular form — in about a third (n = 6; 28.6%).

Today, RMH remains the "gold standard" of radiological diagnostics, since it allows for a differential diagnosis between diffuse and nodular diseases. This is a fast, inexpensive, easily reproducible, objective, operator-independent method [9], which has been positioned in Russian and foreign healthcare for many years as a screening method. The use of RMG as a screening method has led to a significant reduction in mortality from breast cancer [1, 10, 11]. However, despite the obvious advantages, RMG has a number of limitations in certain clinical situations and in a certain group of patients [12, 13]. The generally accepted sensitivity of mammography is 77–95%, and the specificity is 94–97% [9]. The method is not suitable for pregnant and lactating women. When interpreting the results of breast radiology, it is not uncommon for the data obtained using different diagnostic methods to contradict each other, which is due to both objective limitations of informative value and subjective factors, in particular, different interpretations of radiation symptoms. To provide a standardized approach to the interpretation of radiological examinations, the American College of Radiology, in collaboration with other organizations, has developed the

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BI-RADS (Breast Imaging Reporting and Data System). The BI-RADS system provides a systematic approach to the description of breast radiological examinations.

Fine-needle aspiration biopsy and CORE biopsy are invasive, and there are a number of difficulties in their use for mass screening diagnostics. However, only invasive methods under the guidance of echography make it possible to determine the receptor status of the tumor and the level of proliferative activity of tumor cells, which was confirmed in our study.

Immunohistochemical examination made it possible to assess the biological features of the tumor: histological type, degree of malignancy, level of expression of estrogens, progesterone, Her2/new. At the same time, 16 samples were detected: luminal type A — 6 (37.5%), luminal type B — 5 (31.3%), triple negative (basal-like) — 2 (12.5%), luminal B, Her2/new-positive — 3 (18.7%).

Based on the results of the analysis of the data obtained, we estimated the age of patients with breast cancer and determined the prevailing morphological types of tumors. Stage I was diagnosed in 10 (62.5%) of 16 patients with breast cancer. Their average age was 28 years. The second (IIA, IIB) and third (IIIA) stages occurred in 5 (31.3%) women, their average age was 33 years. Stage IV was present in one (6.2%) 34-year-old patient.

Under the age of 35, breast cancer is slightly more common in women with nodular VDM (28.6%) than in women with DPKM (23.8%). The proportion of breast cancer in women with early reproductive life, according to our data, was 18.6%.

A feature of the spread of the breast cancer tumor process was the predominance of infiltrative cancer over infiltrative-ductal cancer (10 (62.5%) versus 6 (37.5%), respectively).

Conclusion

In women of groups I and II, we noted the following risk factors for breast cancer: early menarche, short lactation, multifollicular ovaries against the background of thyroid dysfunction and fat metabolism disorders, as well as a burdened family history.

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