Precancer and vulvar cancer in young women. Are there any features?

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Abstract.
Purpose of the study*: features of the clinical course of precancer and early cancer of the vulva in women of reproductive age.*
Materials and methods: *During the period from 2011 to 2014, 110 patients with dystrophic diseases, precancer and initial cancer of the vulva were examined at the gynecological department of Herzen NMRRC. The age of patients in the study ranged from 18 to 70 years (36±3.5) Two main groups were identified: 1st - pre- and postmenopausal age (from 49 to 70 years) -60 people, 2nd - reproductive age (from 18 to 49 years old) -50 women.*
Results. *In the study of vulvar biopsies, patients with a diagnosis of stage I A vulvar cancer (27%) prevailed in group 1 compared with VIN (vulvar intraepithelial neoplasia) (13%). In group 2, the VIN diagnosis (28%) prevailed in comparison with the invasive tumor process (12%) and was asymptomatic in more than 50% of cases.*
Conclusion. *In women of reproductive age, vulvar neoplasia is more often detected in the form of VIN and in all cases is associated with HPV of high oncogenic risk; in women of pre- and postmenopausal age - at the stage of invasive vulvar cancer,*

rarely associated with HPV (30%). Young patients are characterized by multifocality, and in pre- and postmenopausal age - monofocal lesion.
Keywords: *VIN (vulvar intraepithelial neoplasia), vulvar cancer, women of reproductive age, HPV, multifocal, monofocal.*

This pathology is a visually accessible form of a malignant tumor, however, more than 50% of patients are admitted to a specialized medical institution with common forms of the disease, and its frequency among malignant tumors of the genitals in recent years has increased from 5 to 8% [1,2,3,4,5].

The stable fourth rank place of vulvar cancer in the structure of oncogynecological morbidity creates a false impression of stability and a relatively favorable situation associated with this pathology. The steady increase in the incidence of precancer, intraepithelial and invasive vulvar cancer significantly increases the proportion of this cohort of patients. Meanwhile, now there is every reason to improve the system of early diagnosis and treatment of this pathology [2,5,6,7,8].

No other localization of gynecological cancer has such a close association with postmenopause and involutive-atrophic processes of this period of a woman's life. [6,9,10,11,12,13].

However, over the past ten years, there is evidence of an increase in morbidity in young people, the proportion of which is 15%. The average age of development of the tumor process has decreased from 55 to 35 years, which poses with particular urgency the development of organ-preserving methods of treatment, the use of which is possible only in the early stages of the tumor process (VIN, T in situ, T1) [11,14,15,16, 17.18].

Despite the fact that dystrophic diseases of the vulva are well known to clinicians since the end of the last century, until recently there is no clear and complete understanding of their etiology and pathogenesis. The most well studied and substantiated are the hormonal, viral-infectious (role of HPV) and neuro-endocrine theories.

It would seem that the visual localization of vulvar cancer should serve as a reason for a timely diagnosis. However, every second patient is admitted to a specialized medical institution with stage III-IV disease. In turn, the cause of every second case of advanced cancer is delayed diagnosis. Long-term treatment of background processes without morphological verification of the diagnosis is the main reason for delayed diagnosis. [1,2,6,15,19,20]

The preliminary diagnosis of vulvar pathology is based primarily on specific complaints, data from a thorough examination and additional research methods (vulvoscopy, cytological examination).

During the examination, the mucous membranes are assessed: large and small labia, the degree of hair growth, color, moisture, the presence of pathological elements on the skin.

Vulvoscopy in dystrophic diseases and cancer of the vulva in some cases allows you to detect "suspicious" areas, atypia of blood vessels, in most cases, hyperkeratosis is detected, which limits the diagnostic capabilities of the method. Most often, this diagnostic method makes it possible only to clarify the diagnosis and select sites for biopsy. [5,11,14,19,20,21,22]

In clinically clear cases of cancer, as well as in ulcerative forms of initial carcinoma and melanoma, cytological examination confirms the diagnosis. At the same time, VIN and pre-invasive cancer, in which pathological processes begin in the deep layers of the epidermis, may not be detected by cytological examination.

Unfortunately, in cytological examination, vulvar cancer is confirmed only in 50% of cases, in the rest - dys- and parakeratosis was detected. For the same reason, it is inappropriate to take smears-prints (Pap-smear) for cytological examination from the tissues of the external genital organs.

In the works of foreign researchers on the diagnosis of vulvar diseases, an assessment of the cytological method is given. However, due to the disappointing results (the sensitivity of the method is 32%), the authors emphasize that the gold standard currently remains the histological study of vulvar pathology, the

information content of which is largely determined by the exact choice of biopsy sites. [5,7,11,12,14,21,23]

The purpose of the study is to identify the features of the clinical course of precancer and early cancer of the vulva in women of reproductive age.

Materials and methods

For the period from 2011 to 2014, 110 patients with dystrophic diseases, precancer and initial cancer of the vulva were carried out in the gynecological department of Herzen NMRRC, a full range of examinations with an analysis of clinical features and identification of the sequence of effects of various factors that form the prerequisites for the development of dystrophic diseases and neoplasias of the vulva.

Analysis of outpatient records and case histories of all women allowed us to further study the features of the clinical course of pathological processes of the external genital organs, depending on age.

The age of patients in the study ranged from 18 to 70 years (36 ± 3.5)

All patients were divided into two main groups. The first consisted of patients of pre- and postmenopausal age (from 49 to 70 years), the second - of reproductive age (from 18 to 49 years). When analyzing the age distribution of patients, practically equal cohorts in terms of number were revealed (table № 1):

Distribution of patients by age (table 1).

Groups	Number of patients (abs.)	Number of patients (%)
I.Patients of pre- and postmenopausal age	**60**	**54.5**
II. Patients of reproductive age	**50**	**45.5**
Total	**110**	**100**

Menstrual function was unchanged in 72 (65%) of 110 women. Menarche age ranged from 11 to 18 years (mean age 14.5±0.3 years). The average duration of the menstrual cycle was 28±0.4 days. Thus, there were no significant menstrual dysfunctions.

Most of the patients have repeatedly consulted gynecologists and dermatologists for itching and discomfort in the external genital area. The doctor carried out conservative treatment of "leukoplakia and kraurosis" for many months, and sometimes years, without histological clarification of the diagnosis. More than half (n=78-71%) of patients underwent long-term and unreasonable anti-inflammatory or hormonal therapy with unsatisfactory results without cytological and/or histological studies, aimed only at eliminating symptoms.

The duration of the anamnesis in 54.5% of cases was more than 1 year. During this period, the appointment of various ointments and creams, sedatives, vitamins, hormonal drugs often relieved or reduced itching, discomfort and pain. The patients, feeling relieved, stopped visiting the doctor. Subsequently, 40% had dysplastic processes of varying severity and initial forms of vulvar cancer.

The above indicators serve as a reason for a critical revision of the methods of examining patients with this pathology. Inadequate interpretation of complaints and objective data obtained during the examination of women, insufficient oncological vigilance of doctors and the lack of proper clinical experience for a correct assessment of the condition of the external genital organs leads to an increase in the number of advanced forms of tumor processes.

According to the data of a planned histological examination of vulvar biopsies, in the 1st group of patients, lichen sclerosus was diagnosed in 28 patients (47%), squamous cell hyperplasia - in 8 patients (13%), VIN I - VIN III - in 8 patients (13%), vulvar cancer stage I A was detected in 16 patients (27%) (table 2).

Table 2. Distribution of patients according to the morphological structure of pathological processes of the vulva in the group of patients of pre- and postmenopausal age.

Morphological research data	Number of patients (abs.)	Number of patients (rel.) (%)
Lichen sclerosus	**28**	**47**
Squamous cell hyperplasia	**8**	**13**
VIN I	**2**	**3**
VIN II	**2**	**3**
VIN III	**4**	**7**
Vulvar cancer stage I A	**16**	**27**
Total	**60**	**100**

Thus, in the first group, patients with a diagnosis of stage I A vulvar cancer (27%) prevailed in comparison with vulvar intraepithelial neoplasia (13%). Clinically, early cancer of the vulva presented as a small nodule or warty, cauliflower-like mass. In 2 patients, vulvar lesions were presented as hyperpigmented, light-brown formations rising above the surface.

In 47% of pre- and postmenopausal women, lichen sclerosus was diagnosed, which links this disease with age-related changes in the vulva. The clinical picture of lichen sclerosus was determined by the age and severity of the pathological process. If in the early period of the disease in most patients the mucous membrane was depigmented, whitish in color, then, as the progression progressed, there was a decrease in hair growth in the pubic area and labia majora, the skin and mucous membranes were smoothed, their folding was noted with a violation of elasticity.

The leading symptom (93%) in patients in this group was persistent and painful itching, which in most patients led to disability and a decrease in the quality of life. Most likely, itching is based on violations in the trophism of the tissues of the external genital organs, which lead to thinning, dryness, the appearance of cracks and abrasions due to scratching. Soreness, burning, feeling of dryness, tension and tightening of the skin and mucous membranes were noted. In

patients with a long history of the disease (54.5%), when sclerosis and atrophy became more pronounced, the clitoris and the labia minora were practically undetectable. Large lips in the form of thickened ridges limited the sharply narrowed entrance to the vagina, the mucocutaneous integument became rigid and acquired a pearlescent hue.

According to the data of a planned histological study in the 2nd group - patients of reproductive age - the morphological diagnosis of squamous cell hyperplasia was established in 25 patients (50%), lichen sclerosus - in 5 patients (10%), VIN I –VIN III - in 14 patients (28 %), stage I A cancer - in 6 patients (12%). (table 3)

Table 3. Distribution of patients according to the morphological structure of pathological processes of the vulva in the group of patients of reproductive age.

Morphological research data	Number of patients (abs.)	Number of patients (rel.) (%)
Lichen sclerosus	**5**	**10**
Squamous cell hyperplasia	**25**	**50**
VIN I	**6**	**12**
VIN II	**6**	**12**
VIN III	**2**	**4**
Vulvar cancer stage I A	**6**	**12**
Total	**50**	**100**

Thus, analyzing the data obtained, in the majority of patients of reproductive age, the morphological diagnosis of vulvar intraepithelial neoplasia (29%) prevailed in comparison with the invasive tumor process (12%) and was

asymptomatic in more than 50% of cases. At the same time, itching was the dominant manifestation in the rest of the patients. In more than 60% of women, VIN was multifocal. Clinically, VIN lesions appeared as discrete or confluent painless papules or plaques with uneven margins. On the skin surface, the lesions were presented in the form of whitish plaques with hyperkeratosis, on the mucous membrane - in the form of pink or red papules. It should be noted that the risk of progression of intraepithelial neoplasia (VIN) to invasive cancer in women of reproductive age is rare. It is estimated at about 5%. Consequently, a thorough examination of this contingent of patients allows avoiding the further development of the tumor process. [6,14,24]

Squamous cell hyperplasia was found in 50% of patients of reproductive age. The clinical picture of the latter was represented by itching (n=19-76%), which was less pronounced than in the 1st group, and brought significantly less suffering to patients. Patients complained of the presence of whitish plaques localized on the labia majora, clitoris, in the folds between the labia majora and labia minora, less often occupying the entire surface of the vulva.

If lichen sclerosus is characterized by diffuseness and symmetry of the lesion, which in our study was recorded in 26 patients (93%), then with squamous cell hyperplasia we observed a focal nature of the process. At the same time, the changes in all patients of this group came from different areas of the external genital organs. Its most frequent localization was the labia majora and minora (n=24-73%), less often - the clitoris, posterior commissure, perineum (n=9-27%). The degree of aggressiveness of the course of the vulvar tumor increases from the posterior commissure to the clitoris. [12,13,20,23,25]

The next stage of the study was associated with the study of the infectious component in precancer and initial cancer of the external genital organs. Attention should be paid to the complete absence of examinations aimed at identifying human papillomavirus infection in pre- and postmenopausal women. Usually, a gynecologist at the examination established the diagnosis of "kraurosis of the

vulva" (the terminology of the old classification). The examination was limited to visual examination and the appointment of ointment therapy to relieve itching.

However, at present, many authors associate an increase in the incidence of vulvar cancer with an increase in the number of women suffering from PVI, which indicates the important role of HPV in the multistep process of carcinogenesis. [8,10,15,17,21,26,27,28]

In this study, testing for vulvar HPV DNA by PCR was performed in all 110 patients. Among 60 women of pre- and postmenopausal age, papillomavirus infection was detected in 46 (77%) patients. At the same time, 16 and 18 types were found in 18 (30%) patients; Types 31 and 33 - in 10 (17%) patients; 6 and 11 types - in 18 patients (30%), the absence of HPV - in 14 patients (table 4).

Table 4. HPV typing in pre- and postmenopausal patients.

Virus type	Number of patients (abs.)	Number of patients (rel) (%)
type 16, 18	**18**	**30%**
type 31, 33	**10**	**17%**
type 6, 11	**18**	**30%**
Lack of HPV	**14**	**23%**

Among 50 women of reproductive age, papillomavirus infection was detected in 45 (90%) patients. At the same time, 16 and 18 types were found in 29 (58%) patients; 31 and 33 types - in 10 (20%) patients; 6 and 11 types - in 6 patients (12%), the absence of HPV - in 5 (10%) patients (table 5).

Table 5. HPV typing in patients of reproductive age.

Virus type	Number of patients	Number of patients

	(abs.)	(rel) (%)
type 16, 18	**29**	**58%**
type 31, 33	**10**	**20%**
type 6, 11	**6**	**12%**
Lack of HPV	**5**	**10%**

It should be noted that the presence of human papillomavirus infection in the overwhelming majority of patients was not accompanied by any clinical manifestations.

Thus, the frequency of detection of HPV DNA was largely associated with the age of the examined group. The peak HPV level was observed in young women (90%), while in 78% HPV was represented by types of high oncogenic risk (16,18,31,33) and in 100% it was associated with a malignant process. HPV infection in pre- and postmenopausal patients in this study is quite high (77%), but it is represented by a diverse range of HPV: both high oncogenic risk - 16.18 and 31.33 types (30% and 17%, respectively), and low oncogenic risk -6.11 types (30%), in almost equal proportions. At the same time, VIN and initial vulvar cancer in this group are associated with HPV only in 30% of cases.

In pre- and postmenopausal women, due to the predominance of background dystrophic changes in the form of lichen sclerosus, the morphological diagnosis of VIN of varying degrees is established quite rarely, invasive cancer is more often diagnosed. The analysis of the above allows us to consider lichen sclerosus as a disease preceding cancer of the external genital organs. This contingent of patients must be carefully and comprehensively examined with constant dynamic observation. [20,22,23,25,28]

At the same time, in young patients, the underlying disease is squamous cell hyperplasia, where the sequence of tumor development (VIN I - VIN II - VIN III) is traced more clearly and largely resembles the development of cervical cancer. It was noted that in young women PVI is usually temporary in nature, there is a more

rapid spontaneous elimination of the virus and regression of the existing HPV-associated pathology compared to women of a later age. In this group, HPV types of high oncogenic risk are most often found (16, 18, 31, 33), which account for 78%. Consequently, the inclusion of PCR diagnostics in the examination algorithm of patients with dystrophic processes of the vulva is beyond doubt. The results obtained make it possible to convincingly and purposefully plan measures for the prevention of virus-induced cancer. [10,16,22,24,26,27,28]

Thus, the high frequency of untimely diagnosis of precancer and initial vulvar cancer is due to long-term self-treatment of patients, unjustified anti-inflammatory and hormonal therapy, improper sampling of material for cytological and histological studies, and the lack of oncological alertness among general practitioners. [1,2,6,15,21,23]

Conclusion

The diagnosis of precancer or initial cancer that developed against the background of dystrophic lesions of the vulva is difficult to establish. The existing diagnostic methods are not effective enough, therefore, risk factors (viral infection, biological aggressiveness of the tumor) must be taken into account, which make it possible to select a contingent of patients with pathology of the external genital organs. In this situation, competent planning of diagnostics and its highly qualified implementation plays a decisive role for the patient's fate.

At a young age, the pathology of the vulva is clinically more often manifested in the form of squamous cell hyperplasia, and in the pre - and postmenopausal - in the form of lichen sclerosus.

Based on the foregoing, in women of reproductive age, vulvar neoplasia is more often detected in the form of VIN and in all cases is associated with HPV of high oncogenic risk; in women of pre- and postmenopausal age - at the stage of invasive vulvar cancer, rarely associated with HPV (30%).

One of the features of the clinical course of vulvar neoplasia in women of reproductive age is the characteristic development of several foci of malignancy, which occur synchronously or metachronically. Multifocality of the tumor is an

important unfavorable prognostic factor for the course of precancer and vulvar cancer, which often leads to errors in diagnosis. In patients of pre- and postmenopausal age, the malignant process is more often detected at the stage of a monofocal invasive tumor.

The efforts of scientists from different countries for many decades have been aimed at developing new and effective approaches in the diagnosis of malignant neoplasms of the vulva. By now, considerable scientific and clinical material has been accumulated, however, the results of diagnostics of patients with malignant tumors of the vulva cannot be regarded as satisfactory and require further research.

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