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ORIGINAL ARTICLE

Status and molecular genetic parameters of papillomavirus infection: individual characteristics and associative links with clinical and morphological factors of cervical cancer

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ABSTRACT

Purpose of the study. Study of the characteristics of human papillomavirus (HPV) infection, comparison of HPV status, molecular and genetic parameters of HPV high risk (HR) with the clinical and morphological characteristics of cervical cancer.
Materials and methods. The study included 240 patients with morphologically verified cervical cancer stages I–III, in whom the presence of HPV DNA of 14 genotypes was examined before treatment; upon detection, viral load (VL), the presence and degree of DNA integration into the genome of the host cell were examined.
Results. A number of statistically significant associative relationships have been identified between the molecular and genetic parameters of HPV infection and clinical and morphological indicators of the tumor process, in particular the relationship of HPV-negative CC with age and stage of the disease; HPV infection with several genotypes and HPV genotype – with the histological type of tumor; VL – with age, stage and histological type of tumor. Significant associative connections have been established between the molecular genetic parameters of the virus itself: genotype and level of VL, genotype and integration of HPV DNA into the host genome, as well as a negative linear correlation between VL and the degree of integration.
Conclusion. The obtained data on the relationship between the molecular and genetic parameters of HPV infection and traditional prognostic factors can become the basis for further research on the development of prognostic models for the purpose of personalizing multimodal treatment programs.

Keywords: human papillomavirus (HPV), high carcinogenic risk (HCR), cervical cancer (CC), HPV genotype, multiple infection, viral load, HPV status, virus DNA integration into the cell genome

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Compliance with ethical standards: the work followed the ethical principles set forth in the World Medical Association Declaration of Helsinki, 1964, ed. 2013. The study was approved by the local Ethics committee of the A. F. Tsyb Medical Radiological Research Centre – Branch of the National Medical Research Radiological Centre of the Ministry of Health of the Russian Federation, Obninsk, Russian Federation (extract from the protocol of the meeting No. 103 dated 09/17/2015). All patients signed an informed consent to participate in the study

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3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

Статус и молекулярно-генетические параметры папилломавирусной инфекции: индивидуальные особенности и ассоциативные связи с клинико-морфологическими факторами рака шейки матки

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РЕЗЮМЕ

Цель исследования. Изучение особенностей папилломавирусной (ВПЧ) инфекции, сопоставление ВПЧ-статуса, молекулярно-генетических параметров ВПЧ высокого канцерогенного риска (ВКР) с клинико-морфологическими характеристиками рака шейки матки (РШМ).

Материалы и методы. В исследование были включены 240 больных с морфологически верифицированным РШМ I–III стадий, у которых до начала лечения исследовали наличие ДНК ВПЧ 14 генотипов, при выявлении – вирусную нагрузку (ВН), наличие и степень интеграции ДНК в геном клетки-хозяина.

Результаты. Выявлен ряд статистически значимых ассоциативных связей между молекулярно-генетическими параметрами ВПЧ-инфекции и клинико-морфологическими показателями опухолевого процесса, в частности связь ВПЧ-негативного РШМ с возрастом и стадией заболевания; ВПЧ-инфицирования несколькими генотипами и генотипа ВПЧ – с гистологическим типом опухоли; ВН – с возрастом, стадией и гистологическим типом опухоли. Установлены значимые ассоциативные связи между молекулярно-генетическими параметрами самого вируса: генотипа и уровня ВН, генотипа и интеграции ДНК ВПЧ в хозяйский геном, а также отрицательная линейная корреляция между ВН и степенью интеграции.

Заключение. Полученные данные о взаимосвязи молекулярно-генетических параметров ВПЧ-инфекции с традиционными прогностическими факторами могут стать основой для дальнейших исследований по разработке прогностических моделей с целью персонализации мультимодальных лечебных программ.

Ключевые слова: вирус папилломы человека (ВПЧ), высокий канцерогенный риск (ВКР), рак шейки матки (РШМ), генотип ВПЧ, множественная инфекция, вирусная нагрузка, ВПЧ – статус, интеграция ДНК вируса в клеточный геном

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено локальным этическим комитетом МРНЦ им. А. Ф. Цыба – филиал ФГБУ «НМИЦ Радиологии» Минздрава России (выписка из протокола заседания № 103 от 17.09.2015 г.). Все пациенты подписали добровольное информированное согласие на участие в исследовании

Финансирование: финансирование данной работы не проводилось

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INTRODUCTION

Cervical cancer (CC) ranks first among malignant neoplasms of the female genital organs [1]. Annually, more than 600 thousand new cases are detected in the world and about 342 thousand deaths from this pathology are registered [2]. In the Russian Federation, breast cancer is the leading cause of death from cancer in the female population aged 30–39 years (21.5 %) [3].

Human papillomavirus (HPV) of high carcinogenic risk (HCR) is a proven factor in the development of breast cancer [4]. Among the total number of patients with breast cancer, 88–95 % are HPV-positive, according to various authors [5, 6]. The most common HPV genotypes, according to most literature sources, are types 16 and 18, which are collectively detected in almost 75–85 % of cases of HPV-positive breast cancer [6–9]. In 2020, the World Health Organization introduced a new classification of cervical epithelial tumors based on the presence/absence of HCR HPV, the so-called HPV status [10, 11]. The cited sources indicate that HPV-negative status is an indicator of an unfavorable prognosis of the effectiveness of treatment, but, as noted above, the proportion of such patients is small, which dictates the need to search for prognostic markers in the majority other breast cancer patients with HPV-positive status. It is known that HPV infection is characterized by significant diversity at the molecular genetic level, and, importantly, some of its parameters can affect the sensitivity of tumor cells to antitumor effects (according to the results of studies on cell cultures *in vitro*). In this regard, it could be assumed that studying the features of HPV infection in cervical cancer can provide additional information for stratification of patients in a prognostic aspect, will allow to personalize multimodal treatment programs for breast cancer and, ultimately, improve the effectiveness of treatment.

Data on the relationship between the clinical and morphological characteristics of breast cancer and the molecular genetic parameters of HPV infection are widely presented in the literature. The authors report the presence of an association between HPV status and lymphovascular invasion [12], HPV HCV genotypes and the morphological form of the tumor, the relationship of HPV type 18 with the presence of deep stromal invasion and lymph node damage [13]. Some researchers pay attention to a statistically significant relationship between high viral load (VL) and the risk of metastatic lymph node damage, tumor size [14], others – to the correlation of low VL with the stage of the disease and enlarged lymph nodes [15]. However, the heterogeneity of the samples with the lack of a comprehensive assessment of the relationship of the entire spectrum of molecular genetic parameters of HPV infection with prognostically known clinical and morphological factors often determines the contradictory nature of the data obtained and makes it relevant to further studies in homogeneous groups of patients with breast cancer with the inclusion of the maximum number of criteria studied.

MATERIALS AND METHODS

The study on the topic of HPV infection features, the comparison of HPV status, molecular genetic parameters of HPV HCR with the clinical and morphological characteristics of the tumor process was performed in 240 patients with morphologically verified stage I–III breast cancer (FIGO) who underwent examination and treatment in the department of radiation and combined methods of treatment of gynecological diseases of the A. F. Tsyb Medical Radiological Research Centre – Branch of the National Medical Research Radiological Centre of the Ministry of Health of the Russian Federation, Obninsk, Russian Federation [16]. The study is a retrospective-prospective cohort, conducted in accordance with the protocol approved by the local ethics committee of the A. F. Tsyb Medical Radiological Research Centre – Branch of the National Medical Research Radiological Centre of the Ministry of Health of the Russian Federation, Obninsk, Russian Federation (Protocol No. 103 dated 09/17/2015). The ethical principles set forth by the Helsinki Declaration of the World Medical Association (World Medical Association Declaration of Helsinki, 1964, ed. 2013). Prior to inclusion in the study, the patients signed a voluntary informed consent to participate in the study and determine *in vitro* the parameters of HPV infection in the biomaterial of the cervix. The inclusion criteria were: morphologically verified stage I–III breast cancer, lack of specialized treatment for this disease; non–inclusion criteria – pregnancy, stage IV breast cancer, specialized treatment

for this disease in the anamnesis; exclusion criteria – refusal of patients from further participation in the study. The average age of the patients was 47.2 ± 12.0 years. Locally advanced forms of breast cancer (stages II and III of the disease) prevailed – in total in 186 (77.5 %) patients. According to the morphological structure of the tumor, squamous cell carcinoma of various degrees of differentiation was most often verified in patients – in 216 (90 %). According to the form of growth, endophytic and mixed prevailed, respectively, in 59 (24.6 %) and 136 (56.6 %) patients; according to the variant of the spread of the tumor process, parametric in various variations and metastatic, respectively, in 174 (93.5 %) and 66 (66.7 %) patients.

The presence of HPV DNA of 14 genotypes was studied in all 240 patients before treatment: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68. Biopsies and/or joint scrapings of the epithelium of the cervical canal (endocervix) and the outer wall served as the material for the study cervical surfaces (exocervix) taken before the start of treatment. All stages of the subsequent analysis of the obtained biomaterial samples were performed on domestic test systems produced by the Federal State Budgetary Institution of the Central Research Institute of Epidemiology of Rospotrebnadzor. DNA isolation was carried out by the sorbent method using a set of reagents "DNA-sorb-AM". The presence, differentiated determination of the genotype and quantitative load of HPV was carried out by multiplex PCR with the detection of a fluorescent signal over four channels in real time on the Rotor Gene amplifier (Corbett Research, Australia) using the reagents "HPV Amplification HCR genotype-titer FL". In this test system, the viral genes E1, E6, E7 and the β-globin cellular gene are amplified. Only data for samples with a positive result of β-globin analysis are considered valid. This gene serves as an internal control of the reaction (EQ), and also allows you to estimate the number of cells in a sample (1 cell contains 2 β-globin molecules) and normalize the results of amplification of viral genes for the same number of cells. The results of the study were processed in the Excel software add-in attached to the test system and interpreted in accordance with the following criteria: a) logarithm (lg) of the number of HPV DNA copies per 105 cells less than 3 (VL < 3) – low viral load; b) lg of the number of copies of HPV DNA per 105 cells is equal to or more than 3, but less than 5 (3 ≤ VL < 5) – moderate viral load; c) lg of the number of copies of HPV DNA per 105 cells is more than or equal to 5 (VL ≥ 5) – high viral load. In case of multiple infection, the quantitative load of all established HPV HCV genotypes was determined, the highest indicators corresponded to the leading genotype of the virus.

The presence of HPV DNA integration was assessed by the ratio of the number of genomic equivalents of the E7/E2 virus, taking into account the standard deviation and the coefficient of variation of the data in accordance with the developed algorithm [17]. Its principle is based on the fact that the E7 gene remains intact during the integration of viral DNA into the DNA of the host cell, respectively, its amount in both forms of the virus – episomal and integrated – is the same. In most cases, the E2 gene is destroyed during integration and its amount decreases. The analysis was performed using TagMan technology in real-time multiplex PCR format using a set of reagents that allows differentiated determination of the number of E2 and E7 viral genes and the β-globin cellular gene. In one test tube, sections of the E7 and E2 virus genes and a section of human β-globin DNA, ICS, were amplified. At the same time, standard samples with known concentrations of HPV 16 and 18 DNA and β-globin DNA were amplified in each experiment. All samples, both clinical and standard, were amplified in three repeats. For each of the repeats, the amount of E7 and E2 was calculated using calibration curves and a regression equation obtained on standard samples in accordance with the program for amplification of these genes. The degree of HPV DNA integration was estimated by the formula (1 – E2/E7) × 100 %. The absence of an amplification signal for the E2 gene in the presence of such a signal for the E7 gene corresponds to 100 % integration of viral DNA into the cell genome.

Statistical data processing was performed using the Statistica 10.0 software package (StatSoft, Inc.). For descriptive statistics, average values and standard error (SE) were used. The comparison of groups by qualitative characteristics was carried out using the Fisher criterion, by quantitative characteristics – using the Mann-Whitney U-test. Spearman's nonparametric correlation method with the calculation of the rank correlation coefficient (r) was used to evaluate

the linear relationships between variables. Multivariate analysis was performed using the Agglomerative clustering (AGNES) method with the construction of tree diagrams – dendrograms.

STUDY RESULTS AND DISCUSSION

HPV status and genotype

The presence of HPV HCR was registered in the overwhelming number of patients in the study cohort – in 215 (89.6 %) out of 240. The average age of HPV-infected patients with breast cancer was 46.7 ± 11.8 years, which is much lower than in Europe (54 ± 14 years) [9]. The average age of patients in whom HPV HCR was not detected was 50.6 ± 14.0 years and did not differ from that of HPV-infected patients ($p > 0.05$). However, HPV-negative breast cancer was 3.5 times more common among patients over 55 years of age ($p = 0.004$) (Fig. 1), which is consistent with data from other studies [18, 19]. There was a statistically significant increase in the frequency of HPV-negative forms of the disease at stage III (18.2 %) compared with stages II (3.4 %) and I (7.4 %) (respectively $p = 0.001$ and $p = 0.05$), as mentioned by domestic researchers [18].

Among all the genotypes found in patients with breast cancer, prevailed 16 (62,6 %), 18 (13 %) and 45 (6.1 %) types of HPV HCR, followed by 31 (4,1 %), 33 (2,8 %), 39 and 56 types (2.5 % each) (Fig. 2). The total proportion of other types of HPV HCR (35, 51, 52, 58, 59, 66, 68) It was 6.4 %. A similar share distribution in the countries of the European region, in particular the Russian Federation, is reported in numerous publications, which also indicate the prevalence of HPV genotypes 16 and 18 in 70–75 % of cases [18–20]. In the study group of 215 HPV-positive patients, genotypes or their combinations with the dominant genotype belonging to the phylogenetic group A9 were most often found (16, 31, 33, 35, 52, 58) – in 76.7 % of cases. The share of representatives of the A7 group (18, 39, 45, 59) was more than 3.4 times lower – 22.3 %. The remaining 2 groups A5 (51) and A6 (56, 66) were represented in isolated cases (0.5 %). The peak occurrence of group A9 genotypes occurred at a young age – up to 30 years (78.6 %), and A7 – in the age category up to 45 years (31.3 %), however, without statistically significant differences, which is consistent with the results of multifactorial analysis [21], although some studies demonstrate the presence of a link between the HPV genotype and the age of patients with breast cancer [9].

In squamous cell carcinoma, the prevalence of genotypes of group A9 (80.0 %) ($p = 0.0002$) with the dominance of HPV 16 (74.3 %) ($p = 0.0002$) was noted; in adenocarcinoma, groups A7 (66.7 %) ($p = 0.0003$) with the predominance of HPV 18 (60.0 %) ($p < 0.0001$). HPV type 16 (86 %) was sig-

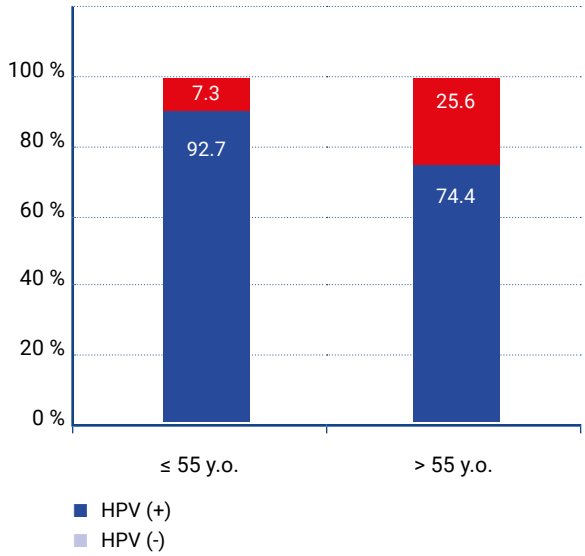

Fig. 1. Features of high risk HPV infection in patients with breast cancer, depending on age

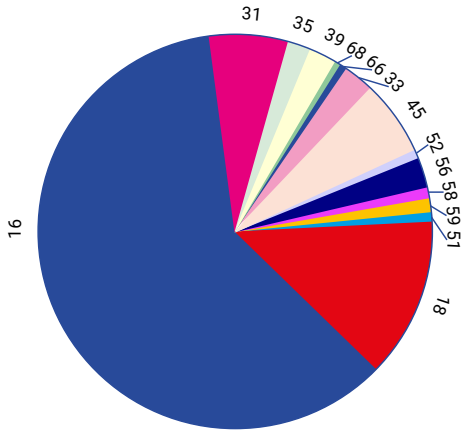

Fig. 2. Prevalence of 14 high risk HPV genotypes in patients with breast cancer, including cases of multiple infection

nificantly more common among HPV 16/18-associated squamous cell carcinomas, and HPV type 18 (64.3 %) in adenocarcinoma (p = 0.0001). A similar associative relationship of phylogenetic groups and, accordingly, genotypes with the histological type of tumor has been revealed in other studies [9, 22]. The distribution of the most common phylogenetic groups (A9 and A7) did not significantly differ depending on the stage of the disease, the form of tumor growth, and in patients with locally advanced breast cancer, including the variant of the spread of the tumor process (presence/absence of infiltration of parametria, metastatic variant) (p > 0.05), which is also confirmed by the results of other research [23].

Infection with several types of HPV HCV (multiple infection) was detected in 25 (11.6 %) of 215 HPV-infected patients (19–2 genotypes, 6–3 genotypes). There were no statistically significant differences in the incidence of single or multiple HPV infection depending on age, stage of the disease, form of growth and variant of tumor spread, which is confirmed in the study by N. Jing et al. (2003) [24]. However, it should be noted that multiple infection occurred only in patients with morphologically verified squamous cell carcinoma (p < 0.0001 when compared with the glandular morphotype of the tumor, p = 0.038 when compared with undifferentiated cancer), this pattern was noticed by other researchers [25].

Viral load

Viral load was determined in 199 HPV-positive patients with stage I–III breast cancer, 175 (87.9 %) of them with a single infection, 24 (12.1 %) cases with multiple infection. In the study group, high VL was most often observed (average level 6.4 ± 1.3) – in 142 (71.4 %) cases. In 50 (25.1 %) patients, VL was moderate (average level 4.4 ± 0.54), and only in 7 (3.5 %) it was low (average level 2.4 ± 0.1). When comparing the data on VL obtained during the processing of various biological materials – cervical scrapings and biopsies of the same patients (n = 47) – a fairly high correlation of these indicators was revealed among themselves (r = 0.72, p < 0.0000001) (Fig. 3).

There was a statistically significant increase in the proportion of cases with low VL with increasing age (r = 0.86, p = 0.04), and no cases of low VL were detected in the age group under 30 years (Fig. 4).

In HPV 16, high virus load was most common, and in HPV 18, moderate and high loads were observed with almost the same frequency (Fig. 5): the average VL level in HPV 16 (6.0 ± 1.7) turned out to be statistically significantly higher than the same indicator in HPV 18 (5.0 ± 1.1) (p < 0.001). This pattern was maintained for the phylogenetic groups to which these genotypes belonged: 6.0 ± 1.6 and 4.9 ± 1, respectively, for the genotypes of the A9 and A7 groups (p < 0.001).

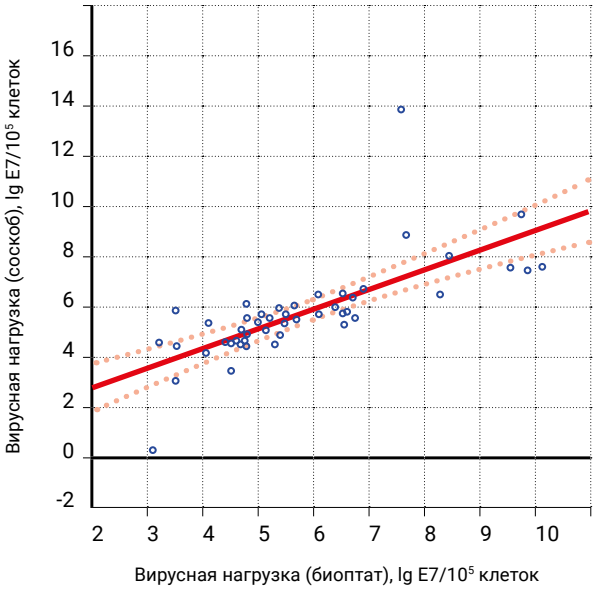

Fig. 3. Analysis of the correlation dependence of the HPV viral load in epithelial samples and corresponding biopsies of the cervix of patients with CC

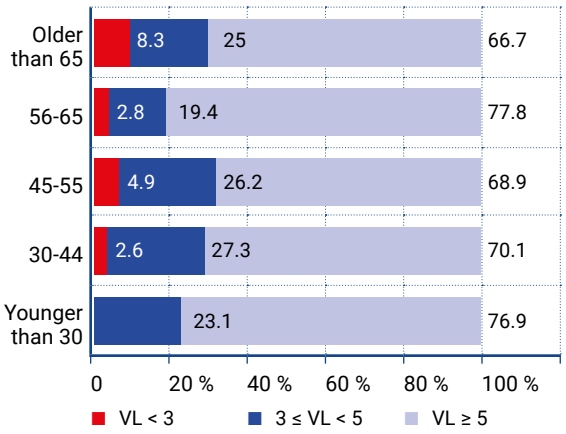

Fig. 4. Viral load (VL) in patients with CC depending on age

In stage III of the disease, the average VL level (6.2 ± 1.6) was significantly higher than in stage I (5.4 ± 1.9) and II (5.4 ± 2.1), respectively, $p = 0.006$ and $p = 0.02$. Our data are consistent with the latest results of domestic studies on relatively low VL in the early stages of the disease [19, 26].

In squamous cell carcinoma, more cases of high VL (73.9 %) ($p = 0.08$) were detected, and in adenocarcinoma – low load (13.3 %) ($p = 0.07$) (Fig. 6). Accordingly, the average level of VL was higher in squamous cell carcinoma (5.8 ± 1.6) compared with adenocarcinoma (5.0 ± 1.6) ($p = 0.10$). The relationship of low load with cervical adenocarcinoma and HPV type 18 is also noted by other authors [27].

According to our data, there were no statistically significant differences in the level of VL in different forms and variants of the spread of the tumor process.

HPV DNA Integration 16/18

The presence of virus DNA integration, both complete and partial, was studied in patients infected with HPV types 16 and 18 (140 and 28 cases, respectively), which are the most aggressive and account for the vast majority of all genotypes detected in breast cancer. Such patients accounted for 78.1 % of all HPV-positive cases in our study. In the studied cohort, the majority of patients revealed the integration of virus DNA (integrated form) – in 101 out of 168 people (60.1 %), which confirms the results of a number of studies on the high incidence of invasive PCV virus in the integrated state [26, 28]. In the remaining 67 (39.9 %) patients, there was a lack of integration of HPV DNA into the cellular genome (episomal form according to the criterion of preserving the E2 gene in an intact state). It should be noted that the failure to integrate HPV DNA into the genome of the host cell in accordance with the algorithm described above cannot be unambiguously interpreted as the presence of only the episomal form of the virus, since such integration can occur with the participation of various other viral genes [29–30]. However, this process is mainly associated with a violation of the integrity of the E2 gene of the virus [31], which is explained by the high availability of this viral gene for various types of genetic rearrangements. Moreover, we have obtained data suggesting a higher biological significance of the E2-mediated pathway of integration of the viral genome into the cellular one, as opposed to integration invoVLing other viral genes [32].

A comparative analysis of the data on the degree of integration of viral DNA in scrapings and biopsies of the cervix obtained from the same patients ($n = 47$) revealed a fairly high correlation of the indicators with each other: the correlation coefficient $R = 0.89$ at a significance level $p < 0.000001$ (Fig. 7).

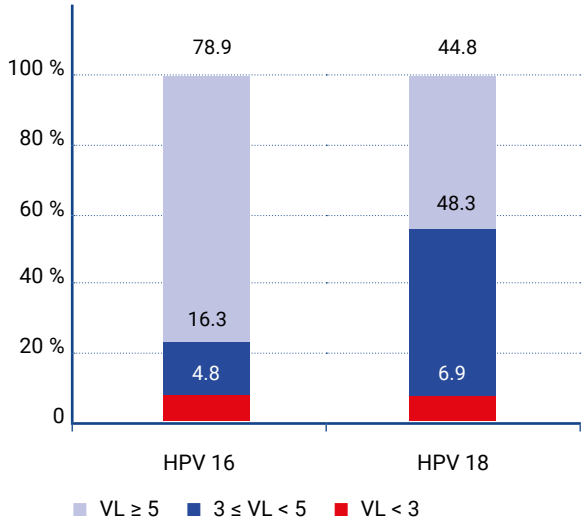

Fig. 5. Viral load (VL) in HPV-positive patients with CC, depending on the genotype of the virus

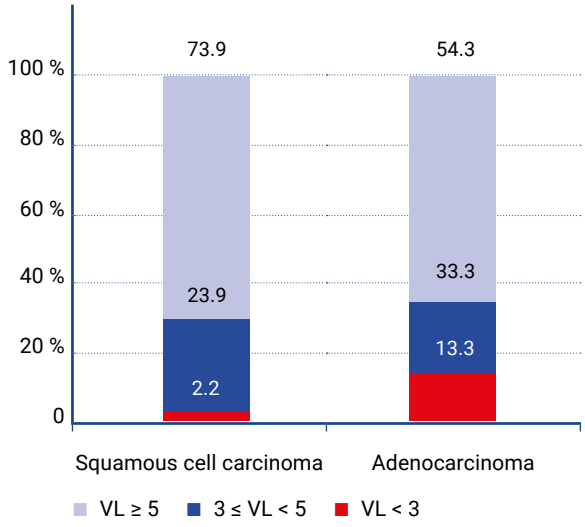

Fig. 6. Viral load (VL) in HPV-positive patients with CC depending on the morphological form of the tumor

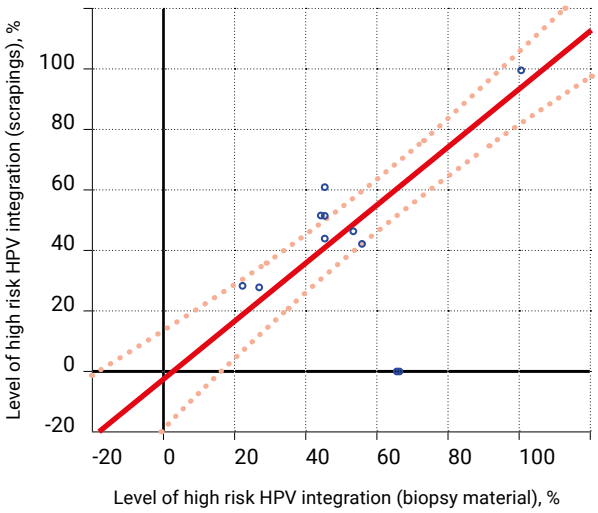

Fig. 7. Analysis of the correlation dependence of the degree of high risk HPV integration in epithelial scrapings and corresponding biopsies of the cervix of patients with cervical cancer. The degree of integration varies from 0% (the episomal form of the virus) to 100 % (full integration of viral DNA into the cellular genome). The intermediate values correspond to the mixed form of high risk HPV– the presence of both episomal and integrated forms; the quantitative indicator – the degree of integration corresponds to the proportion of integrated forms of high risk HPV

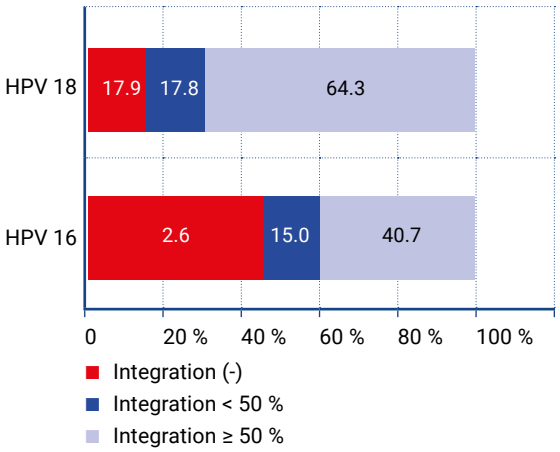

Fig. 8. Physical status and degree of integration of HPV 16 and HPV 18 DNA in patients with CC

Table 1. Distribution of CC patients depending on the qualitative and quantitative parameters of HPV 16/18

Viral form	Episomal abs (%)	Integrated abs (%)	
Viral load		< 50 %	≥ 50 %
VL < 3 (*n* = 5)	1 (20.0)	0	4 (80.0)
3≤ VL < 5 (*n* = 39)	11 (28.2)	5 (12.8)	23 (59.0)
VL ≥ 5 (*n* = 124)	55 (44.4)	21 (16.9)	48 (38.7)

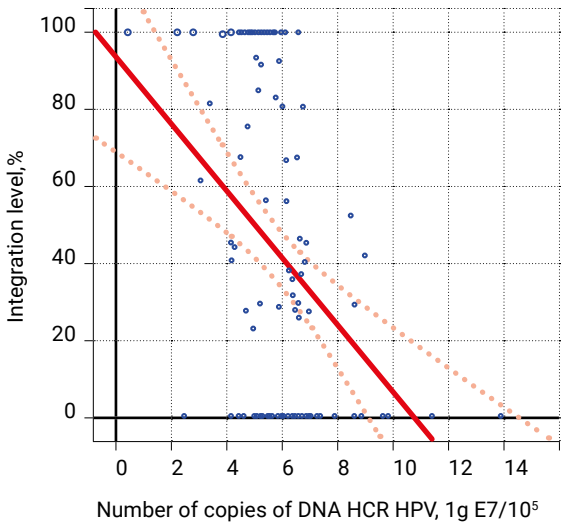

Fig. 9. Correlation analysis of the molecular genetic parameters of HPV infection in CC patients (n = 168): 0 % – lack of integration (episomal form of the virus), 100 % – complete integration of HPV DNA into the genome of the host cell. The intermediate values correspond to the mixed form of HCR HPV – the presence of both episomal and integrated forms; the quantitative indicator – the degree of integration – corresponds to the proportion of integrated forms of HPV 16/18

Taking into account these data, as well as similar results of a comparative analysis of HCV, it is possible to recommend the use of scraping of the cervical epithelium for the molecular genetic study of HPV parameters, since the informative value of the material obtained by this method is not inferior to the informative value when performing a more traumatic procedure – cervical biopsy.

The integrated form of HPV HCR was most common in patients over 65 years of age – in 66.7 % of cases, while in 44.4 % of cases it was in the form of complete (100 %) integration. When infected with HPV 18, compared with HPV 16, integrated forms of the virus prevailed (82.1 % and 55.7 %, respectively, p = 0.01) with a predominance of highly integrated (DNA integration ≥ 50 %) forms (64.3 % and 40.7 %, respectively, p = 0.019), a high percentage of which was full (100 %) integration HPV DNA (50.0 % vs. 20.7 %, p = 0.003) (Fig. 8). The more frequent detection of HPV type 18 in the integrated state compared with HPV type 16 is also reported in foreign studies [33].

The analysis of the presence/absence and degree of integration depending on clinical and morphological characteristics did not reveal statistically significant associative relationships, which is consistent with the literature data [34].

Associative relationship of viral load and HPV DNA status 16/18

The molecular genetic parameters of viral infection were studied in 168 HPV 16/18-positive patients with stage I–III breast cancer. As the HCV increased, there was an increase in the proportion of episomal and a decrease in the proportion of highly integrated forms of the virus (Table 1).

Low viral load only in a single case (20.0 %) accompanied the liposomal form of the virus; all other cases of low viral load (80.0 %) were combined with 100 % integration. Previously, we had established an inverse linear correlation between VL and the degree of integration of HPV DNA into the cellular genome [35]. Subsequently, the sample of patients was significantly increased, and this pattern remained with high significance (r = – 0.41, p < 0.0001) (Fig. 9).

Multivariate analysis

In order to study possible associative relationships between various parameters characterizing the tumor process and HPV infection, a multidimensional exploratory analysis was performed using the clustering method, which allowed us to identify the most interrelated parameters – the morphological form of the tumor and HPV status (Fig. 10), and in HPV-positive breast cancer – the morphological form

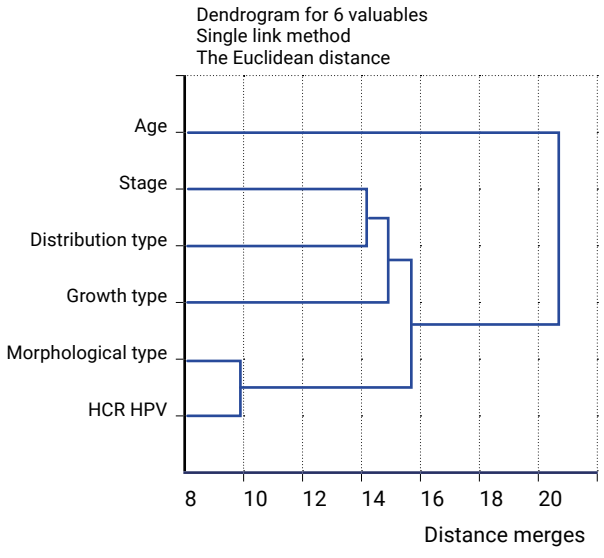

Fig. 10. Dendrogram of CC patients with HPV status (n = 240)

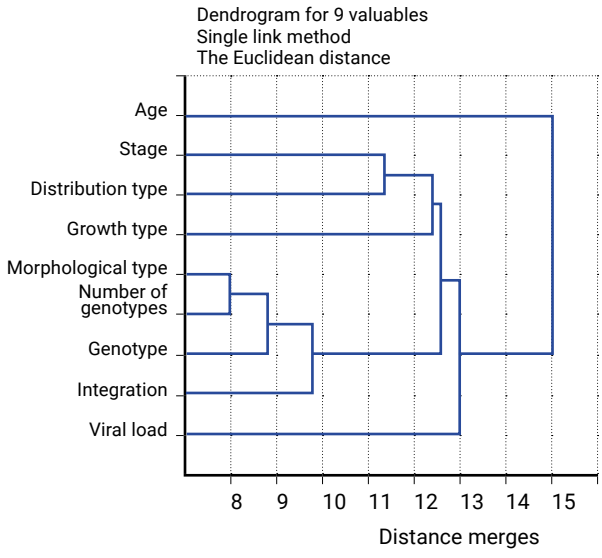

Fig. 11. Dendrogram of HPV-associated CC patients taking into account the entire spectrum of molecular genetic parameters of HCR HPV (n = 174)

of the tumor and the following features of HPV infection: the number of HPV HCV genotypes present, genotypes 16 and 18, the physical status of viral DNA – the presence/absence of integration into the genome of the host cell (Fig. 11).

Thus, multifactorial exploratory analysis made it possible to detect associative relationships that were not obtained by pairwise comparison of various factors, but which could be assumed indirectly when studying the results of a single-factor analysis.

CONCLUSION

The study of possible associative relationships between a wide range of molecular genetic parameters of HPV infection and the clinical and morphological characteristics of a malignant tumor of the cervix revealed the presence of correlations between HPV status, HPV genotype, the number of genotypes present and a known prognostic factor – the morphological form of cervical cancer. At the same time, our work shows the absence of a relationship between such molecular genetic parameters of HPV infection as the genotype and the level of integration of virus DNA into the cellular genome with the main traditional factor in predicting the effectiveness of treatment – the stage of the disease. This fact suggests the possibility of a prognostic value of these parameters independent of the stage and justifies the expediency of conducting further studies to assess the prognostic value of the level of integration of HPV DNA of various genotypes (primarily the most common types 16 and 18) as potential independent biomarkers for predicting the effectiveness of treatment of breast cancer.

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Kiseleva V. I. – optimization of molecular and genetic research methods, analysis of the results obtained and maintenance of the database, participation in writing and editing the text of the article;
Krikunova L. I. – planning the clinical part of the study, discussion of the obtained clinical data;
Boyko B. V. – collection and design of literature, translation of the text into English;
Gusarova V. R. – collection and analysis of literature;
Bezyaeva G. P. – collection and processing of biological material, conducting PCR studies for the presence of HCR HPV DNA;
Panarina L. V. – collection and processing of biological material, conducting PCR studies for the presence of HCR HPV DNA;
Ivanov S. A. – scientific editing and approval of the final text;
Kaprin A. D. – scientific summary;
Zamulaeva I. A. – development of the concept and scientific design of the study, interpretation of the obtained clinical and experimental data, scientific editing of the article, summarizing the results obtained, formulation of conclusions.