L.N. Afanasyeva, E.V. Filippov, G.V. Filippova, P.V. Nikiforov, T.I. Nikolaeva, N.A. Larionova, M.S. Struchkova DETECTION OF HIGH-RISK HUMAN PAPILLOMA VIRUS IN WOMEN WITHIN THE FRAMEWORK OF THE SECOND STAGE OF THE PILOT PROJECT "OHKOПOИCKCAXA.PФ" IN YAKUTIA

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The study was conducted in 2022 as part of the implementation of the second stage of the pilot project "OHKOΠO//CKCAXA.PΦ" (ONCO-SEARCH) at the Yakut Republican On-cology Dispensary, which is part of the national project "Healthcare". The project involved 798 women from 10 districts of the Republic of Sakha (Yakutia). The comprehensive examination included cytological testing, detection and genotyping of high carcinogenic risk human papillo-mavirus (HCR-HPV) using polymerase chain reaction, and assessment of viral load. The territori-al distribution of HCR-HPV types was demonstrated. The overall infection rate among women ranged from 6.9% (Tomponsky district) to 25.0% (Oymyakon district), with an average of 14.8%. The majority of infections were of the episomal - non-integrated form of HPV. Differ-ences in infection rates among women of different age groups were observed. The highest pro-portion of HCR-HPV carriers, including integrated forms, was found in the age groups

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of 20-30 and 31-40 years. High-grade squamous intraepithelial lesions (HSIL) were diagnosed in 2.5% of the examined women, while low-grade squamous intraepithelial lesions (LSIL) were found in 1.8%. One woman was diagnosed with squamous cell carcinoma. The study showed a correlation between viral load, integrated forms of HPV, and cervical intraepithelial neoplasia (CIN). The integrated form of genotype 16 made the largest contribution (50%) to CIN lesions among HCR-HPV-infected individuals.

Keywords: human papillomavirus, screening, age distribution, integrated forms, cervical cancer, cervical intraepithelial neoplasia.

Introduction. Human papillomavirus (HPV) is one of the most common sexually transmitted infections in Russia and many other countries [5, 7]. High-risk HPV is capable of integrating its genome into human DNA and rapidly spreading, leading to cell transformation and the development of malignant tumors [9,13,14,17]. Studies conducted in different regions of the world have shown that HPV is the main risk factor for cervical cancer (CC) development. Epidemiological observations conducted in numerous areas confirm this association [6, 8]. Cervical cancer is a relatively common disease among women, ranking fourth in terms of cancer incidence worldwide. In Russia, according to data from 2021, cervical cancer accounted for 4.9% of all cancers in women [4].

The main methods of combating cervical cancer include vaccination, screening, diagnosis, and subsequent treatment with assessment of treatment outcomes. The most optimal strategies to combat this disease are mass vaccination of girls before the age of 15, periodic screening of older women, and subsequent treatment in case of detection of morphological changes in tissues [23].

Early-stage treatment is more effective and can only be achieved through periodic screening, as women generally do not exhibit symptoms and there are no reasons for examination. Screening not only leads to more effective treatment outcomes but also proves to be more cost-effective overall, as the costs of preventive screening are significantly lower than expensive future treatments. Cervical screening involves diagnostic tests using cytology and PCR methods to detect morphological changes [12].

To determine type-specific risk and predict disease incidence, it is necessary to study the geographical distribution and characteristics of HPV types, as well as investigate infection rates in the region. This is because HPV infection rates can vary by region, and therefore, preventive and treatment algorithms may differ [6, 8].

The Yakut Republican Oncology Dispensary has launched the pilot project "ONKOPOISKSAKHA.RF" as part of the national project "Healthcare". In 2021, the first stage of mass HPV screening for women in Yakutia was conducted. Medical teams traveled to different settlements and regions to examine the population and collect samples for laboratory testing. In the first stage, 724 women from 5 districts (Zhigansky, Verkhoyansky, Churapchinsky, Namsky, Srednekolymsky) of the Republic of Sakha (Yakutia) and the city of Yakutsk with its suburbs were examined. The studies determined the overall infection rate, identified differenc-



es in infection rates among women of different age groups, and demonstrated the territorial specificity of different HCR-HPV genotypes distribution [2]. However, a significant part of the regions remained uncovered, and in some indicators, such as infection rates in the age groups of 20-30 and over 70 years, the sample size needed to be expanded for statistical significance.

The Purpose of the Study: To continue mass screening testing, including cytological examinations, analysis of HPV genotype distribution, and characteristics of viral load of 14 oncogenic HPV types in women residing in 10 districts of the Republic of Sakha (Yakutia) that have not been previously covered by the study.

Material and Methods. In the voluntary screening study of the second stage of the pilot project "ONKOPOISKSAKHA. RF," women residing in 10 districts of the Republic of Sakha (Yakutia) participated. These districts include Allaykhovsky, Anabarsky, Verkhnekolymsky, Gorny, Lensky, Neryungrinsky, Oymyakonsky, Tomponsky, Ust-Maysky, and Khangalassky. The age range of the participants was from 20 to 87 years (n = 798). The average age of women in the final overall sample was 48.0±9.6 years.

The material for the study consisted of epithelial cells collected from cervical and cervical canal swabs, which were placed in a liquid-based cytology transport medium. The collected material was analyzed using liquid-based cytology on an automated system called CellPrepPlus (Korea). The slides with the biomaterial were stained using the Papanicolaou method. The results of liquid-based cytology were interpreted according to the Bethesda System terminology (2014).

For DNA extraction, the "AmpliSens® DNA-Sorb-D" kit was used, which is designed for total DNA extraction. For simultaneous amplification and detection of HPV DNA regions (multiplex PCR), the "AmpliSens® HPV VKR Screen-Titer-14-FL" test system was used. This test system allows for the detection of 14 highly oncogenic types of HPV:

• for genotypes 16, 31, 33, 35, 52, 58 – region E1 gene

• for genotypes 18, 39, 45, 56, 59, 66, 68 – region E2 gene

• for genotype 51 - region E7 gene

The E6 gene region was detected separately for genotypes 16, 18, and 45 (Table 1). The detection of the E6 region in the absence of the E1/E2 region indicated viral integration into the human genome. The presence of the E6 region in the presence of the E1/E2 region was interpreted as a mixed form, while the absence of the E6 region in the presence of the E6 region in the presence of the E1/E2 region indicated a non-integrated, episomal form of the virus.

To determine the genotype and viral load concentration, the "AmpliSens® HPV HCR Genotype-Titer-FL" reagent kit was used. Amplification was performed on a 6-channel real-time PCR detection system with a 96-well block, the "Real-time CFX-96 Touch" from Bio-Rad (USA). The amplification setup and analysis of the obtained results were conducted using the "FRT-Manager" software (version 3.7). The obtained result with a specific viral load concentration was interpreted according to the instructions (Table 2).

The statistical analysis of the data was performed using the "Statistica" 6.0 software. To determine the statistical significance of differences in the distribution of frequencies of qualitative variables between groups, a four-fold contingency table analysis was used [24]. The level of significance was determined using the x2 (chi-square) test. The strength of the association between the risk factor and the outcome was assessed using the normalized value of the Pearson coefficient (C'). The risk assessment of the outcome based on a binary variable was performed using the odds ratio (OR) with a 95% confidence interval.

Results and Discussion. The overall prevalence. It is known that the prevalence of HPV in Russia is approximately 20-30%. However, different studies have shown highly variable results between regions and social groups, indicating a focal nature of HPV transmission [7]. Previously, using the example of 5 districts of the Republic and the city of Yakutsk, we showed that the overall prevalence of HPV HCR among women can vary across geographical areas, ranging from 4.7% to 11%, which is a difference of more than 2 times [2].

Table 1

Distribution of Fluorophores by Detection Channels

Channel for Fluorophore	FAM	JOE	ROX	Cy5	Cy5.5
Target DNA	HCR HPV DNA Genotype 16	HCR HPV DNA Genotype 18	Genotypes 16,18,31,33,35, 39,45,51,52,56, 58,59,66,68	Plot DNA β -Globin Gene (Internal Control Sample Glob)	HCR HPV DNA Genotype 45
Amplification Region	E6 Gene	E6 Gene	E1 Gene (for genotypes 16, 31, 33, 35, 52, 58)/ E2 gene (for genotypes 18, 39, 45, 56, 59, 66, 68)/ E7 gene (for genotype 51)	β-Globin Gene	E6 Gene

Table 2

Interpretation of lg results (HPV per 100,000 cells)

Virus concentration, HPV genome equivalents, n*lg/10^5 cells	Interpretation	
<3	Clinically insignificant value	
3–5	Clinically significant value. Dysplasia cannot be ruled out, there is a risk of developing dysplasia	
>5	Clinically significant, elevated value. High chance of dysplasia	

HPV HPV HΡV Negative, Total. Ulus (Village) HCR² Mixed (Geno-types), Persons Infected, Per-sons/(%) 45¹ Persons/(%) 161 181 Persons 9 Allaihovsky $1(18^{1}.52^{2})$ 78 88 10 (11.4) 1 (16¹.51²) 7 Anabarscy 1 _ _ 52 62 10 (16.1) 1 (161.392.562. 312. 592) 7 9 (14.8) Verhnekolymsky 1 1 52 61 2 19 111 133 22 (16.5) Gorny 9 3 1 13 1 (161.181.451) 125 152 27 (17.8) Lensky 2 Nerungrinsky 2 37 42 5 (11.9) 1 Oimyakonsky 1 3 15 20 5 (25.0) 1 _ Tomponsky 2 27 29 2(6.9)Ust-Maisky 4 17 1 (16¹.51².16²) 135 157 22 (14.0) Khangalassky 1 5 48 54 6(11.1) 2 5 798 Total: 21 6 84 680 118 (14.8)

Structure of HCR HPV Infection

1 – genotypes – region E6 gene (likely integrated into the human genome);

2 - genotypes 16, 31, 33, 35, 52, 58 - E1 gene region, genotypes 18, 39, 45, 56, 59, 66, 68 - E2 gene region, geno-type 51 - E7 gene region.

In the studies conducted during the second stage of the pilot project "ОНКОПОИСКСАХА.РФ" (2022), HPV HCR infection was detected in 118 women, with a prevalence rate of 14.8% (n=798) (Table 3). Among the 10 districts of the Republic of Sakha (Yakutia) that were studied, the highest prevalence rates were observed in the following districts: Oymyakonsky - 25.0%, Lensky - 17.8%, Gorny - 16.5%, and Anabarsky - 16.1%. The lowest prevalence rate was found in Tomponsky district, where it was 6.9%. However, due to the small sample size of n=20 for Oymyakonsky and n=29 for Tomponsky districts, it is expected that the prevalence values will be adjusted when expanding the number of participants in future studies.

The integration of HPV DNA into the human cell DNA structure is a key event in the transformation of infected cells [10]. The integrated form of the virus stimulates cell proliferation, induces genomic instability, and can lead to the development of mutations [18,19,22]. The most frequently integrating HPV genotypes are 16 and 18, where the E1/E2 region is disrupted but the oncogenes E6/E7 are preserved [15, 21]. Thus, cervical cancer is a unique example of virus-associated carcinogenesis, where the constant presence of exogenous HPV genetic information in tumor cells plays an important role in their transformation.

Figure 1 shows the distribution of integrated HPV HCR forms and overall virus infection rates across districts. The average infection rate across the 10 districts was 14.8%, with integrated virus forms accounting for 4.3% of cases.

The highest proportion of integrated

virus forms was observed among the surveyed women in the Oymyakonsky (10%), Lensky (9.2%), and Neryungrinsky (7.1%) districts. Interestingly, cases of co-infection with two or more HPV HCR genotypes, combined with integrated forms, were recorded among women from 4 districts (Table 3). In Allaykhovsky district, a combination of integrated HPV-18 and non-integrated episomal HPV-52 forms was detected. In Anabarsky and Ust-Maysky districts, combined infection of integrated HPV-16 forms with episomal forms was found. In Lensky district, there was one case of infection with three integrated virus forms of genotypes 16, 18, and 45. It should also be noted that among all the surveyed women, the prevalence of the episomal (non-integrated) form of virus infection (HCR², Table 3) with detectable E1/E2/E7 gene region of HPV HCR predominates.

The age structure of infection. The dependence of infection and disease prevalence on the age of the surveyed individuals is of particular interest in sci-



Fig. 1. Structure of the Territorial Distribution by Uluses of General Infection and HPV Forms Integrated into the Human Genome (%)

Table 3



entific research on virus prevalence. It is believed that virus prevalence correlates with the age range of active sexual life [11,20]. The highest peak of virus infection is observed in the age group of 15-20 years. The peak of precancerous cervical conditions is registered with a shift of 10 years, and the peak of the prevalence of invasive cancer occurs at the age of 40-50 years [20]. In Yakutia, according to research, the peak incidence of cervical cancer is observed in the age group of 40 to 54 years [1], which generally corresponds to global indicators.

To identify age-related distribution patterns of HPV in the Republic of Sakha, we combined data from 2022 with the results of studies from 2021 [2]. To understand the age structure of the distribution among all surveyed individuals, further analysis was conducted based on 6 age groups (Fig. 2). The largest proportion of surveyed women was in the age group of 41-50 years, accounting for 30%. The smallest groups were women aged 20-30 and over 70 years, accounting for 6.5% and 4.1%, respectively. Considering that screening examinations were conducted after widespread public awareness through mass media and were voluntary in nature, the highest medical participation in the «ΟΗΚΟΠΟИСКСАХА.ΡΦ» program was observed among women aged 41-50 years, while medical passiveness was more prevalent among women aged 20-30 and over 70 years.

The analysis of HPV HCR distribution showed that the highest proportion of carriers was observed among women aged 20-30 years (16.7%) and 31-40 years (10.7%) (Fig. 3). The lowest infection rate was observed in the group aged over 70 years, accounting for 6.8%. As mentioned earlier, the study had smaller sample sizes in the younger (20-30 years) and older (over 70 years) age groups, with n=162 and n=103, respectively.

The maximum proportion of integrated HPV HCR forms was also found in the age groups of women aged 20-30 years (6.2%) and 31-40 years (3.6%). In descending order, the next groups were women over 70 (2.9%), 41-50 (2.7%), 51-60 (2.2%), and the lowest number of cases (0.5%) of integrated virus forms were detected in women aged 61-70 years, which generally corresponds to global indicators.

Cervical intraepithelial neoplasia (CIN). The studies conducted using liquid-based cytology (n=798) identified intraepithelial lesions of various degrees (CIN) in 35 women (4.3%). Among them, 14 (1.8%) were diagnosed with low-grade squamous intraepithelial lesions (LSIL),

and 20 (2.5%) had high-grade squamous intraepithelial lesions (HSIL) of the flat epithelium (Table 4). One woman (0.13%) was diagnosed with morphological changes characteristic of squamous cell carcinoma. The age of women with detected intraepithelial lesions of various degrees ranged from 20 to 63 years. In terms of age distribution, the highest proportion of CIN was found in the 20-30 age group, accounting for 9.1%, while the lowest proportion of CIN changes was observed in women over 60 years old (1.1%). In the other age groups, the proportion of CIN did not differ statistically: 31-40 years (5.0%), 41-50 years (4.8%), 51-60 years (5.1%).

To determine the relationship between HPV HCR infection and intraepithelial lesions, a comparative analysis of the obtained results was conducted. Among HPV-positive women (n=118), the number of women with morphological changes in the cervix was 14 (11.9%), while among HPV-negative women (n=680), it was 21, or 3.1%. The differences between the groups were statistically significant (p<0.001); the odds ratio (OR) with a 95% confidence interval (95% CI) was 4.22 (0.158-0.667). Thus, HPV HCR-infected women have more than a 4-fold higher risk of developing intraepithelial lesions of the flat epithelium.

without screening, the average mortality rate from cervical cancer is 8.3 cases per 1000 women. However, systematic cervical screening can reduce this rate to 0.76 when using cytological examination and to 0.29 when utilizing HPV testing as the primary analysis. Despite the high sensitivity of PCR testing, our data confirms the necessity of comprehensive screening that includes both PCR testing and cytological screening.

High viral load can be used as a prognostic risk factor for the development of cervical intraepithelial neoplasia (CIN) and cervical cancer. In the two cases of detected CIN changes and in the case of diagnosed squamous cell carcinoma, high viral loads (>3 genome equivalents) were observed in HPV-positive women, which are interpreted as clinically significant (Table 2), indicating a risk of developing dysplasia. In 10 cases, the viral load was >5 genome equivalents, indicating a high likelihood of dysplasia development. In the entire sample of HPV-positive women, a viral load >3 genome equivalents was detected in 36 surveyed women. Statistical analysis of the four-fold contingency table showed a significance level of p<0.001 based on the x2 (chi-square) criterion. The measure of association between the risk factor (concentration >3 genome equivalents) and the outcome (intraepithelial le-

The study [16] demonstrates that



Fig. 2. Structure of the Distribution of the Studied by Age Groups (%)





Y-Axis: Infection (%)

HCR HPV	(n)/genotypes	Detection region	Quantity HPV genome equivalents, n*lg/10^5 cells				
Low-grade squamous intraepithelial lesion (LSIL)							
HPV-18	1	E2	5.2				
HPV-31	2	E1	5.0/5.7				
HPV-39	1	E2	5.6				
Negative	10	-	-				
High-grade squamous intraepithelial lesion (HSIL)							
HPV -16	4	E6	4.7-6.3				
HPV -31	1	E1	6.2				
HPV -51	1	E7	4.7				
HPV-16/ HCR	(1) / HPV 16/39/56/31/59; (1) / HPV-16/51/16; (1) / HPV-16/51	E6/ E2/ E1/; E6/ E7/ E1; E6/ E7	4.8/3.8/5.2/6.0/3.3; 6.1/4.2/5.3; 6.1/5.8				
Negative	11	-	-				
Squamous cell carcinoma							
HPV-51	1	1 (E7)	4.7				

Prevalence of infection in women with detected intraepithelial lesions

sions) had a strong association strength (C' = 0.685). Our findings confirm a direct correlation between high viral concentrations and the risk of developing cervical intraepithelial lesions of various degrees.

In the study [3], the authors provide data indicating that high viral load of HPV-16 increases the probability of its integration into the cellular genome. From our obtained data (Table 4), it can be seen that in 7 out of 14 cases of CIN in HPV-positive women, HPV-16 is diagnosed in an integrated form (detected in the E6 gene region), both as a mono-infection (4 women) and in mixed forms with episomal variants (3 women). Other HPV genotypes detected in women with CIN were relatively rare. For example, HPV-51 was detected in two cases, including squamous cell carcinoma, HPV-31 and HPV-39 in 3 and 1 case, respectively. In the statistical evaluation, three cases of mixed genotypes, including integrated (HPV-16) and episomal forms of the virus, were classified as integrated forms due to the predominance of this risk factor. In the overall sample of HPV-positive women, genotype 16 was detected in 40 cases, with 25 of them in an integrated form (Table 3). The analysis of the obtained data showed a level of statistical significance (p < 0.05). The measure of association between the risk factor (integrated form of HPV-16) and the outcome (intraepithelial lesions) was relatively strong, with C' = 0.475. Thus, based on the results of our study, the maximum contribution to the structure of

detected HPV genotypes associated with cervical lesions was made by genotype 16 in an integrated form.

As a result of implementing the first and second stages of the pilot project "ONKOPOISKSAKHA.RF," we obtained data for the first time on the prevalence of HPV HCR, including integrated forms, in 15 districts of the Republic of Sakha. The association between HPV HCR infection and the risk of developing cervical intraepithelial neoplasia and cervical cancer was investigated. In order to obtain more accurate statistical data in areas with insufficient population coverage and to study the prevalence of the virus across the entire territory of the Republic of Sakha (Yakutia), further continuation of mass screening HPV testing is required, expanding the geographic scope of the research

Conclusion. It has been established that the overall infection rate in the 10 studied districts ranges from 6.9% to 25%, with an average of 14.8%. The highest infection rates were found in the Anabar district - 16.1%, Gorny district -16.5%, Lensky district - 17.8%, and Oymyakon district - 25.0%. The maximum proportion of integrated forms of the virus was observed among surveyed women in the Oymyakon district (10%), Lensky district (9.2%), and Neryungri district (7.1%). In terms of prevalence, the most common integrated genome forms were HPV genotype 16 (2.6%), followed by HPV 18 (0.8%) and HPV 45 (0.25%).

According to the aggregated results

for 2021-2022, the highest proportion of HPV HCR carriers was found in the age groups of 20-30 years (16.7%) and 31-40 years (10.7%). These same age groups also had the highest proportion of integrated forms of the virus, at 6.2% and 3.6%, respectively. The lowest number of cases (1.0%) of integrated forms of the virus was observed in the age group of 61-70 years, and the lowest infection rate was found in women over 70 years old. The highest participation in the survey was among women aged 41-50 years (30%), while the lowest participation was among women aged 20-30 years (6.5%) and over 70 years old (4.1%).

Among the surveyed women, a high grade (HSIL) of squamous epithelial lesions was diagnosed in 2.5%, a low grade (LSIL) in 1.8%, and one woman (0.13%) was diagnosed with squamous cell carcinoma. The maximum proportion of CIN was found in the age group of 20-30 years, accounting for 9.1%, while the minimum proportion of CIN changes was observed in women over 60 years old (1.1%). It has been shown that HPV HCR infection increases the risk of intraepithelial squamous epithelial lesions by more than 4 times. A direct correlation between viral load and integrated forms of HPV with cervical intraepithelial neoplasia has been identified. The integrated form of genotype 16 contributes to 50% of CIN lesions among HPV HCR -infected women.

All identified cases of infection, with a high probability, can lead to cervical

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cancer. All infected individuals have been registered and referred for further investigation and treatment at the Yakut Republican Oncology Dispensary under the pilot project "OHKOΠO/ICKCAXA.PФ".

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