COMPARATIVE ANALYSIS OF THE RESULTS OF TESTING CERVICAL EPITHELIAL SAMPLES AND CERVICAL BIOPSY SPECIMENS FOR HPV

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Currently, testing for human papillomavirus (HPV) DNA is more and more often used as a primary diagnosis method when conducting screening for cervical cancer. However, HPV genotypes reported when assessing cervical smears can differ from the results of testing cervical biopsy specimens. The study aimed to assess the features of detecting HPV DNA in the paired cervical canal epithelium samples and cervical biopsy specimens. HPV-positive patients (n = 99) underwent targeted cervical biopsy. The HPV DNA was detected 175 times in biomaterial obtained from the cervical canal and 111 times in histologic blocks. In the group of patients with chronic cervicitis, the rate of HPV DNA testing results match was 28.3%, in the group with LSIL it was 45%, and in the group with HSIL it was 67.7%. When the HPV viral load was low, the results were matched in 27.1% of cases, when the viral load was moderate in 35.4%, and when the viral load was high these were matched in 82.3% of cases. We revealed a relatively strong correlation between the viral load and the probability of the HPV test results match: the percentage of HPV DNA test results match between paired samples increases by 9.3% with the increase in the HPV viral load by 1 lg.

Keywords: HPV testing, HPV viral load, cervical pathology, cervical biopsy

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Compliance with ethical standards: the study was approved by the Ethics Committee of the Kulakov National Medical Research Center for Obstetrics, Gynecology and Perinatology (protocol No. 11 dated 25 November 2021) and conducted in full compliance with the requirements for confidentiality of personal dara, ethical standards and principles of conducting medical studies involving humans stated in the Declaration of Helsinki of the World Medical Association “Ethical principles for medical research involving human subjects”.

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СРАВНИТЕЛЬНЫЙ АНАЛИЗ РЕЗУЛЬТАТОВ ВПЧ-ТЕСТИРОВАНИЯ В ОБРАЗЦАХ ЦЕРВИКАЛЬНОГО ЭПИТЕЛИЯ И БИОПСИЙНОГО МАТЕРИАЛА ШЕЙКИ МАТКИ

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В настоящее время при проведении скрининга на рак шейки матки в качестве первичного метода диагностики все чаще применяют тестирование на ДНК ВПЧ. Однако генотипы вируса папиломы человека (ВПЧ), регистрируемые при исследовании цервикальных мазков, могут отличаться от результатов тестирования в биоптированных фрагментах шейки матки. Целью исследования было изучить особенности детекции ДНК ВПЧ парных образцов эпителия цервикального канала и биопсийного материала шейки матки. ВПЧ-позитивным пациенткам (n = 99) была выполнена прицельная биопсия шейки матки. Регистрация ДНК ВПЧ произошла 175 раз в биоматериале, полученном из цервикального канала, и 111 раз в гистологических блоках. В группе пациенток с хроническим цервицитом показатель совпадения результатов тестирования на ДНК ВПЧ составил 28,3%, для группы с LSIL — 45%, для группы с HSIL — 67,7%. При низкой вирусной нагрузке ВПЧ соответствие результатов наблюдалось в 27,1% случаев, при умеренной вирусной нагрузке — в 35,4%, при высокой вирусной нагрузке — в 82,3%. Обнаружена относительно сильная корреляционная связь между уровнем вирусной нагрузки и вероятностью совпадения результатов ВПЧ-тестирования: при увеличении уровня вирусной нагрузки ВПЧ на 1 lg наблюдается увеличение процента соответствия результатов тестирования на ДНК ВПЧ между парными образцами на 9,3%.

Ключевые слова: ВПЧ-тестирование, вирусная нагрузка ВПЧ, патология шейки матки, биопсия шейки матки

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Cervical cancer (CC) is the second most common tumor found in women of reproductive age [1]. Human papillomavirus (HPV) was proven be a mandatory prerequisite for most malignant neoplasms (MN) of the cervix [2, 3]. In recent years, most countries have changed the paradigm of national CC screening programs and chose HPV testing over cytological examination as a more sensitive method. Up to 90% of HPV infections are transient: the virus self-eliminates within 1–2 years [3, 4]. However, in 10% of cases, it persists, and sometimes cause development of a tumor [5, 6]. The global prevalence of HPV varies from 43% to 72.8% [7, 8]. In the USA alone, more than 14 million new cases of HPV infection are registered every year [9]. It should be noted that the development CC is preceded by squamous intraepithelial lesions of the cervix. Among HPV-positive women, low-grade squamous intraepithelial lesions of the cervix (LSIL) occur in 11.5% of cases, while 10.3% of them suffer from high-grade squamous intraepithelial lesions (HSIL) [10].

Currently, the detection of DNA of HPV directly in the affected cervical tissue is perceived as an important marker of viral activity that is fundamentally important for the prognosis of the likelihood of development of precancerous and cancerous lesions of the cervix [11–13]. The detection of HPV in a histological sample is a reliable sign of the level of contamination because the said sample originates from the affected part of the tissue, where the registered virus of a certain genotype and in a certain amount acts as the etiological cause of the pathological process. However, there is still no accurate understanding of the difference between finding DNA of HPV in a cervical smear and in a cervical biopsy.

This study aimed to investigate the specifics and patterns peculiar to the detection of DNA of HPV in the paired cervical canal smears and cervix histological samples.

METHODS

For this cross-sectional study, we used the biological material from 99 HPV-positive patients who sought cervical pathology diagnosing at the Scientific Outpatient Department of the V. I. Kulakov National Medical Research Center for Obstetrics, Gynecology and Perinatology from January to December 2023. In the context of the comparative analysis aimed at learning the diagnostic value of detecting HPV DNA, the genotype of the virus was identified in a pair of samples taken from each participant, one being the secretions of the cervical canal, another — cervix biopsy (colposcopy-guided). All patients were divided into three groups depending on the histological verification of the diagnosis:

1) Group 1 — diagnosed with LSIL (n = 34);

2) Group 2 — diagnosed with HSIL (n = 31);

3) Group 3 — diagnosed with chronic cervicitis (n = 34) (control group).

The inclusion criteria were: age 18–65 years; HPV-positive status confirmed by the cervical canal secretion test; LSIL, HSIL, chronic cervicitis confirmed by the histopathological examination of the cervix biopsy.

The exclusion criteria were: pregnancy, lactation; malignant neoplasms of the cervix; non-specific inflammatory diseases at the decompensation stage.

In the context of this single-stage cross-sectional study, all patients underwent the following:

1) medical history taking, clinical examination (general and bimanual examinations);

2) real-time PCR testing for DNA of HPV using a diagnostic panel with 21 HPV genotypes (6, 11, 16, 18, 26, 31, 33, 35, 39, 44, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82);

3) extended colposcopy to visualize a potentially pathological area of the cervical epithelium for subsequent targeted cervical biopsy;

4) cytological examination (liquid-based cytology);

5) colposcopy-guided cervical biopsy followed by histological verification of the diagnosis;

6) identification of DNA of HPV, its genotyping and assessment of the viral load by real-time PCR (in histological samples).

For the real-time PCR test for DNA of HPV, we used an array designed to detect 21 genotypes of HPV. The materials for the test were cervical canal secretion samples and cervix bioptates harvested under CT guidance. The bioptates were fixed in neutral buffered formalin (pH = 7.0) for 24 hours. After

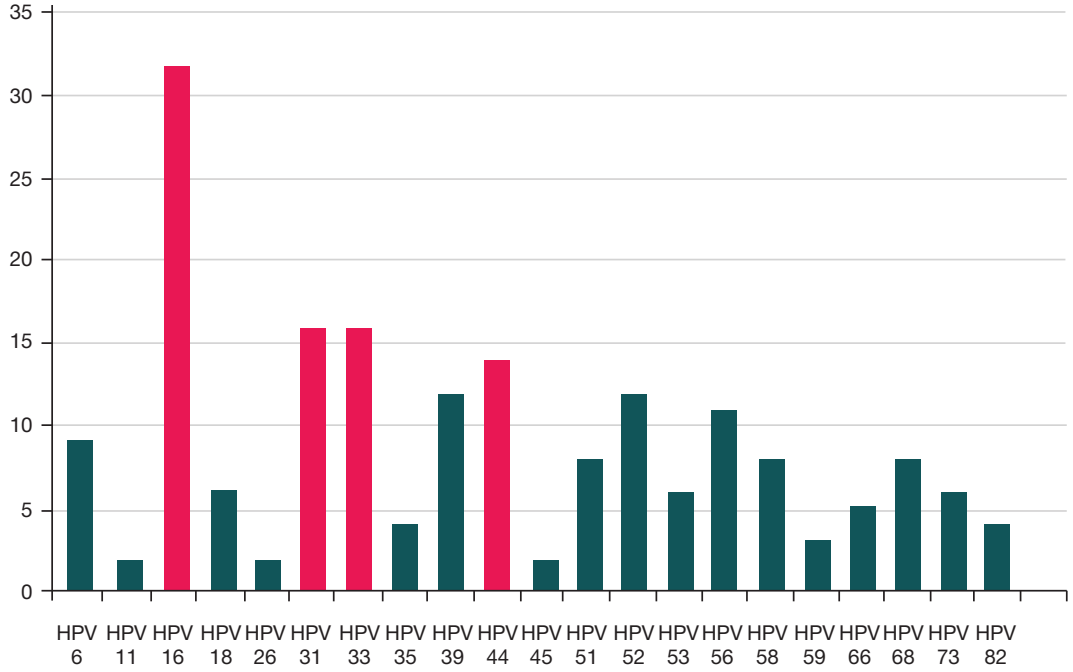

Fig. 1. Distribution of HPV genotypes in cervical canal smears

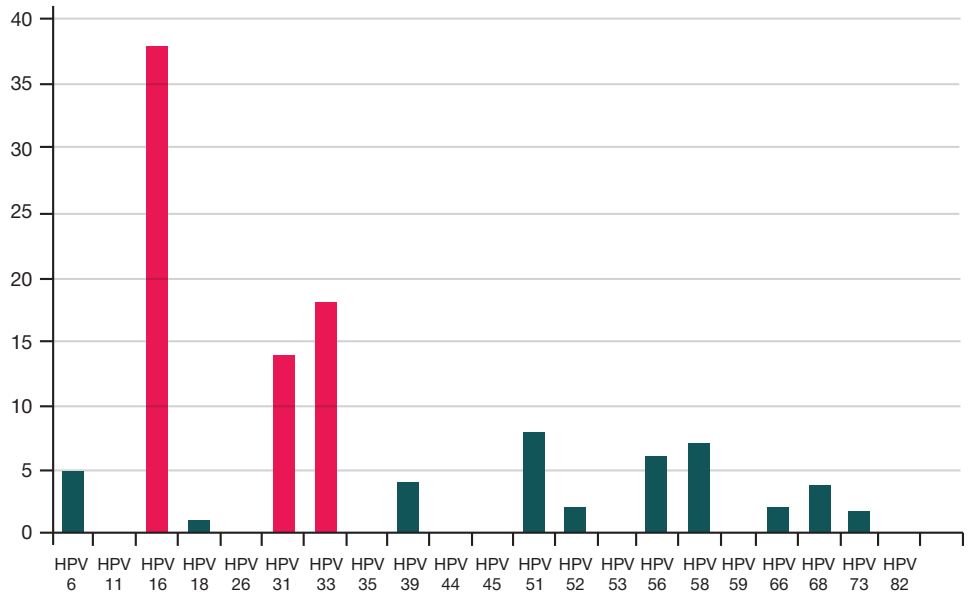

Fig. 2. Distribution of HPV genotypes in the biopsy specimens

fixation, the samples were put into Histo-Tek VP1 (Sakura, Japan) for tissue processing, and semi-automatic paraffin embedding station (Leica HistoCore Arcadia, Germany) was used to form paraffin blocks. Paraffin sections 5 μm thick were put into 1.5 ml dry tubes and transported for HPV DNA testing, same as the tubes with the cervical canal secretion samples. To prevent compromising of the results of comparison of HPV DNA identification in smears and bioptates, all samples were harvested within a single menstrual cycle. Before DNA isolation from the bioptates, paraffin was removed and samples treated with proteinase K using the Proba-PK kit (DNA Technology, Russia), then we isolated the DNA with the help of the Proba-NK kit that precipitates nucleic acids in alcohol. The viral load in the range from 0 to 3.0 lg was regarded as low, in the range from 3.1 to 5 lg — moderate, and values from 5.1 lg and up were considered to represent a high viral load [14].

Statistical data processing methods

For statistical data analysis, we used the IBM SPSS Statistics Version 20 software package (IBM, USA). The normality of distribution of the variables (under the Gaussian law) was checked with the help of the Kolmogorov–Smirnov test. At this step, it was established that most variables do not distribute normally, therefore, as is customary for data violating the Gaussian law, we used the median, which is less susceptible to extreme variations. The dispersion measures were represented by the upper and lower quartiles (Me (Q_1; Q_3)). Categorical data were presented as a percentage with a 95% confidence interval (95% CI) calculated using the Wilson method. Nonparametric Mantel-Haenszel chi-square value tests were used to compare variables depending on their properties (quantitative or categorical). The level of significance was set at $p < 0.05$.

RESULTS

Among the 99 pairs of samples, we registered DNA of HPV in 175 cervical canal smears and 111 biopsy specimens. In the smears, the distribution was as follows: chronic cervicitis — 53/175 (30.3%), LSI — 60/175 (34.3%), HSIL — 62/175 (35.4%). In the biopsy specimens, this characteristic was less uniform: chronic cervicitis — 22/111 (19.8%), LSIL — 40/111 (36.0%), HSIL — 49/111 (44.1%). A noteworthy fact is that in the biopsy samples from patients diagnosed with chronic cervicitis and HSIL, we registered HPV DNA significantly less frequently than in the secretion samples paired with the respective biopsy specimens ($p = 0.048$ and $p = 0.034$, respectively). We have also considered the distribution of HPV genotypes through the lens of the method of sampling (Fig. 1, 2). For 25/111 (22.5%) cases of HPV DNA detection in the biopsy specimens, we failed to find identify HPV genotypes in the paired smears. In 8/25 (32%) of such cases, the registered genotype was HPV-16, in 7/25 (28%) cases — HPV-33, and in 6/25 (24%) cases — HPV-51. It is important to note that HPV-16 was most frequently identified in the biopsy specimens of the patients from Group 1 (6/8, 75%).

The comparative analysis has revealed that in 49.1% of cases HPV DNA was detected in both the cervical canal smears and the paired cervical biopsy specimens. It is also important to take into account the intra-group overlap of the HPV testing data. In Group 3 (chronic cervicitis), the level of coincidence of detection of HPV DNA in both samples of the pair was 28.3%, in Group 1 *(LSIL) — 45%, in Group 2 (HSIL) — 67.7% (Fig. 3).

One of the important components of this study was the assessment of the prevalence of simultaneous detection of two or more HPV genotypes. Several HPV genotypes were detected in 46/99 (46.5%) of the cervical canal smears. However, the respective tests made on the biopsy specimens returned only 13/99 (13.1%) of such cases. This difference is statistically significant ($p < 0.001$).

Analyzing the correlations between HPV test results, we discovered a noteworthy phenomenon. HPV-44, which is one of the three most prevalent genotypes (14/175. 8%) and is more associated with HSIL than with LSIL or chronic cervicitis (50% vs 28.6% vs 21.4%, respectively), was not detected in of the cervical biopsy specimens. At the same time, for other most common types, the matches within the pairs were frequent: HPV-16 — 30/32 (93.8%), HPV-33 — 13/16 (81.3%), HPV-31 — 11/16 (68.8%) (Fig. 4).

The aspects of the study that are of particular interest are investigation of the effect of HPV viral load on the various indicators, such as the incidence, frequency of simultaneous detection of several genotypes, and the degree of cervical

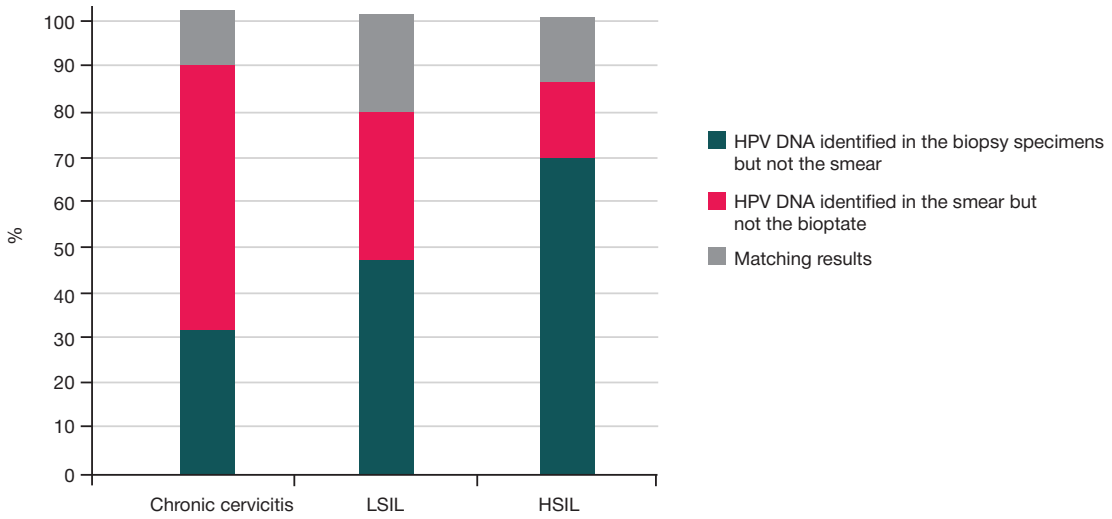

Fig. 3. Coincidence of registration of HPV DNA in both samples of a pair (comparative analysis)

lesion. In particular, we analyzed how the amounts of HPV affect the frequency of matching results in sample pairs. Among cervical canal smears, 62 exhibited high HPV viral load, 65 — moderate, and 48 low viral load. Among the biopsy specimens, the distribution was as follows: high viral load — 52 samples, moderate viral load — 37 samples, low viral load — 23 samples. It should be borne in mind that 22.5% of HPV DNA detections in the biopsy specimens were first-time, which means that these cases were not factored into the calculation of correlations between quantitative HPV test results. The analysis has shown that when the viral load is low, the results of the HPV DNA detection tests matched in 27.1% of sample pairs, when the load was moderate — in 35.4% of the pairs, and when it was high, 82.3% of sample pairs exhibited matching results (Fig. 5). It is important to note that the differences in the amounts of matching results in high vs. moderate viral load, and in high vs. low viral load cases was significant ($p < 0.001$ for both comparisons). Cramér's V showed a relatively strong correlation between the level of viral load and the probability of matching HPV test results (Table). Comparison of the frequency of matching HPV DNA detections in moderate and low viral load cases revealed no significant differences ($p = 0.456$).

In addition, we calculated the correlation of HPV test results depending on each viral load range, taking 1 lg as the increment. It was established that an increase of 1 lg raises the probability of confirmation of infection with the HPV genotype detected in the cervical canal smear (in an initially determined quantitative ratio) by 9.3%.

DISCUSSION

There are very few studies dedicated to this subject. For our study, we took as a reference an experiment that paired 74 paired cytological and histological samples of cervical cancer and tested them using a 51 HPV genotype diagnostic array [13]. In that experiment, the HPV test results matched in 93% of cases, but when the viral load was low, the results differed in 78% of cases. In addition, two or more types of HPV were detected significantly less often in bioptates than in smears (14% vs 47%; $p < 0.001$). It should be noted that the results of our study confirm and largely complement these findings. In Group 2 (HSIL), the proportion of matching results of HPV DNA tests was 67.7%, in Group 1 (LSIL) — 45%, and in Group 3 (chronic cervicitis) is was 28.3%. The values reported by the authors of the mentioned experiment support the upward

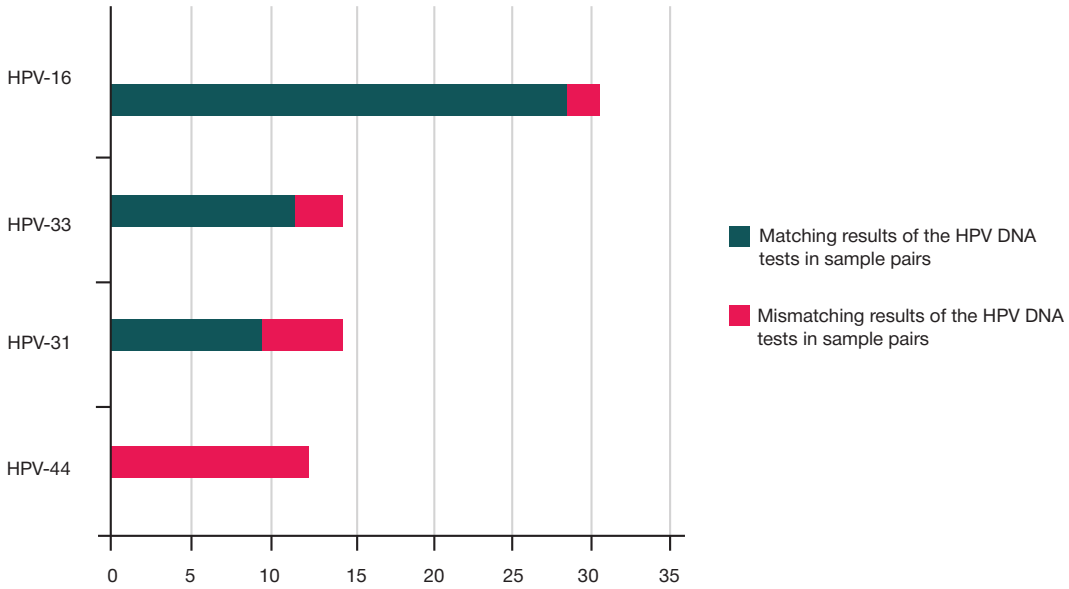

Fig. 4. Comparative analysis of the most common HPV genotypes, cervical canal smears and cervix biopsy specimens

Table. Correlation of the level of viral load and the proportion of matching HPV DNA detections in the sample pairs

Gradation of HPV viral load	Matching test results cases	Mismatching test results cases	Cramér's V	*p* value
High/low viral load	51/13	11/35	0.555	$p < 0.001$
High/moderate viral load	51/23	11/42	0.445	$p < 0.001$
Moderate/low viral load	23/13	42/35	0.074	$p = 0.456$

trend reflecting the dependence of the amount of matching results on the degree of damage to the cervix, which we registered. Our analysis shows that when the HPV viral load is low, the detection results in the sample pairs match in 27.1% of cases, when the load is moderate, this value goes up to 35.4%, and in high viral load circumstances, it increases to 82.3%. This is also consistent with what was reported in the foreign study. Another noteworthy aspect in which our findings coincide with those reported in the referenced experiment concerns registration of several HPV genotypes in a single sample: we encountered such situations significantly less often in cervix bioptates than in the cervical canal smears (13.1% vs 46.5%; $p < 0.001$). It is also important to note the specific distribution of HPV-44 we have identified: this genotype was the most common in cervical canal smears, but it was not found in any of the cervix bioptates. This probably indicates that HPV-44 has a tropism for columnar epithelial cells. Given the results of our retrospective study, which demonstrate the association between this genotype and precancerous condition of the cervix, HPV-44 should probably be studied further.

CONCLUSIONS

Thus, increasing HPV viral load translates into a growing probability of detection of HPV genotypes in the diseased cervical tissue. In addition, the amount of matching results of HPV tests in paired samples depends on the pathomorphological conclusion: the more severe the cervical lesion, the more likely HPV is to be detected in the bioptates.

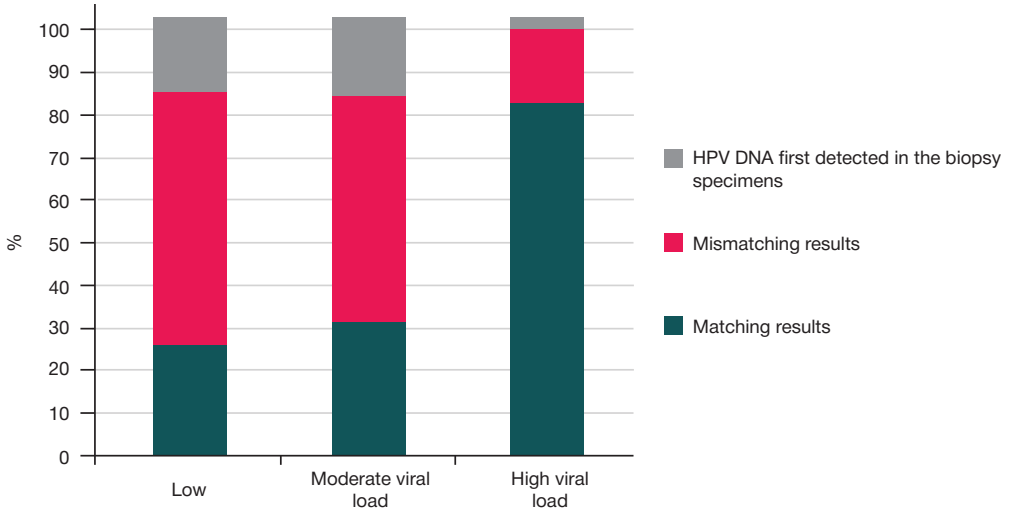

Fig. 5. Comparative analysis of HPV test results based on the established viral loads

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