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ORIGINAL ARTICLE

HPV-ASSOCIATED DISEASES AND THEIR CYTODIAGNOSIS

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Abstract. Introduction: *Conventional cytodiagnosis (PAP) has been used since the 1950s as a method for cervical cancer (CRC) prevention. Through the PAP smear test, the presence of persistent HPV infection could be proven, which cytopathologists described as the presence of koilocyte changes, a consequence of the nuclear membrane destruction.* ***The objective*** *of the present study has been to present the relevance of the conventional PAP smear as a method for the diagnosis of HPV-associated precancerous and cancerous diseases of the cervix.* ***Materials and Methods:*** *During the period 2019-2021, a retrospective study was carried out covering 128 female patients from Hinkomed MC LTD and Sv. Marina University Multi-Profile Hospital for Active Treatment (UMPHAT) LTD, Pleven. The obtained data were processed with MS Office Excel 2019 software.* ***Results:*** *The covered group of patients was divided into two, according to the obtained results from the PAP smear test. The first group consisted of 74 patients (57.8%) with PAP I-II results (not signaled – cytologically). HPV-associated disease was diagnosed in 74.5% (38 patients) of them, and cervical inflammation in 13 (25.5%). The second group included 54 female (42.2%) with a PAP IIIa result and a higher group, called cytologically signaled. The study proved that 2 of the cases (3.7%) were false positive, 21 of the cases were true negative. There were 46 true positive cases and 39 false negative cases.* ***Conclusion:*** *The PAP smear test has been insufficient for the diagnosis of HPV-associated precancerous and/or cancerous diseases of the cervix. As an independent diagnostic method, it has been used only for HPV infection detection.*

Key words: *screening, PAP, HPV*

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INTRODUCTION

Human papillomavirus (HPV) has caused the most common sexually transmitted infections worldwide. The rapid rate of the virus spread has defined it as a burden for global and public health [4].

In the 1970s, Prof. Zur Hausen established the relation between HPV and cervical cancer. The German virologist confirmed the hypothesis that the viral infection found in condyloma acuminate might lead to cervical cancer development. For this discovery, the author was awarded with the Nobel Prize [35].

Based on the evidence of Zur Hausen, various researchers had identified screening as the main method to reduce the scope of HPV-associated diseases. It was of crucial significance for the rapid and timely diagnosis of the most serious disease of this group – cervical cancer. Therefore, the preventive programs developed worldwide were related only to it, and not to the entire group of HPV-associated diseases. It would be worthy to note that screening programs had been also the basis of the efficient treatment, because they supported rapid diagnosis even with hidden morbidity [28].

Conventional pap smear (PAP test), liquid-based cytology, colposcopy, DNA HPV tests and pinch biopsy had been used in the diagnosis of HPV-associated diseases.

Conventional cytodiagnosis (also called the PAP test) has been used since the 1950s as a method for the prevention of cervical cancer (CRC). The method was developed in 1928 by the pathologist George Papanicolaou and was introduced as a new technique in 1943 [1, 2]. He defined it as easy for both technical and practical skills [3, 9].

Papanicolaou gave a simple scientific explanation for the proof of CRC, namely that in malignant cells a different nuclear morphology, called aberrant, was observed, which was the basis for distinguishing a benign from a malignant cell [3].

The PAP test was a non-invasive, inexpensive and widely used screening method globally. It had been also the main method for diagnosing pathological deviations in the cellular morphology of the cervix [3].

As Zur Hausen proved, the human papillomavirus (HPV) was considered to be the main causative agent of CRC. The persistent infection caused nuclear lamina destruction, which in turn changed the cell nuclei morphology. These deformities were detectable by the PAP test, although they could not be typified. The main disadvantage of the conventional smear was the lack of possibility to typify the proven HPV infection [7].

The PAP test had been used as a popular screening method, which was introduced in Bulgaria in 1974. Currently, every female, aged 30 – 40 had been entitled to such a test, which was regulated in the activities of the general practitioners (GPs) in Appendix 12 of the National Framework Agreement for preventive medical checks for persons over 18 years of age. The frequency of the oncologic prophylactic smear was annual for women between 30 and 40 years old, and if two negative results were obtained, the periodicity was changed to once every 3 years [3].

For comparison, in the US, screening was recommended to start at age 21. The frequency recommended by the American Cancer Society was every 3 years for women aged 21-29. In the age group 30-65 years, the PAP frequency was kept at 3 years, but if undergoing a DNA test for HPV, it was increased to 5 years [17].

The obtained materials and results of conventional cytology were classified and interpreted according to the PAP scale. It consisted of 5 groups. The classification was presented in detail in table 1 [8].

Table 1. Papanicolaou classification

Result	Interpretation
I group Normal result	Presence of normal cells
II group Normal to atypical	Presence of atypical cells without evidence of malignancy
III group Suspect result	Presence of atypical cells suspect for malignancy
IV group Suggestive result	Presence of atypical cells suggestive of malignancy
V group Indicative result	Convincing cytological evidence of malignancy

Adapted to: Cirkel C, Barop C, Beyer DA. Method comparison between Munich II and III nomenclature for Pap smear samples. J Turk Ger Gynecol Assoc. 2015

The analysis of the reference sources showed that PAP test was an inexpensive, accessible, non-invasive widely distributed method that had improved the diagnosis of cervical cancer [7].

Liquid-based cytology was a non-invasive method that reduced the number of inadequate and false-negative results. The cellular sample was taken from the cervical canal and the portio, using a soft brush, and then placed in a container with liquid medium. The advantage of the test was that the sample could be kept for 8 weeks at room temperature without the need for further processing [24, 28, 30].

If abnormal results were obtained, a DNA analysis might be done from the liquid. The results were classi-

fied according to Bethesda, and the last revision was made in 2014, presented in detail in table 2 [2, 25].

Table 2. Classification according to Bethesda system

BETHESDA result	Interpretation
MILM	Negative cytology
Presence of atypical cells	
ASCUS	Of unclear cell significance
ASC-H	Atypical cells, suspected high-grade lesion (HSIL)
LGSIL-LSIL	Low-grade intraepithelial lesion
HGSIL-HSIL	High-grade intraepithelial lesion
AGC – NOS	Presence of unspecified atypical cells
AGS – neoplastic	Presence of suspicious atypical cells
AIS	Adenocarcinoma in situ

Adapted to: Nayar, R. and Wilbur, D.C. (2015), The Pap test and Bethesda 2014. Cancer Cytopathology

The similarities and differences between conventional and liquid-based cytology were significant. In this regard, a comparison was made of the results of the two scales presented in table 3.

Table 3. Comparison of the conventional and liquid-based cytology results

Result per PAP	Result per BETHESDA
I group Normal result	NIML
II group Normal to atypical	NIML
III group Suspect result	LSIL, HSIL
IV group Suggestive result	HSIL
V group Indicative result	AIS, Invasive carcinoma

Adapted to: Nayar, R. and Wilbur, D.C. (2015), The Pap test and Bethesda 2014. Cancer Cytopathology

Liquid-based cytology had been more precise, mild and high degree of the cervix dysplasia, even Ca colli uteri in situ might be diagnosed with it (Table 2). However, economically, it was less profitable as it was a more expensive method compared to the PAP test [24, 31, 32].

The study by Rauf et al. had been in support of the cited literature. They concluded that cervical cancer screening programs, including primary screening methods such as PAP tests, human papillomavirus (HPV) DNA tests, and/or liquid – based cytology, might detect early stages of cancer. The authors argued that effective prevention programs would improve the morbidity and mortality rates of CRC [27].

DNA tests focused to typify the virus, i.e. to determine whether it was a high- or low-risk type. It was possible to be performed together with a pap smear, because the test was taken from the cervix. Only genital infection was typified by this method. The test only identified a current infection and could not show the type of virus in a previous one. Demonstration of a high-risk HPV type would require close clinical monitoring of the patient [34].

DNA tests could be used as a primary screening test for HPV-associated diseases or as an addition to conventional Pap smear. The joint approach was defined as better regarding the evidence of cervical pathologies [6, 19, 24].

Colposcopic examination had been a leading diagnostic method for pathologies of the cervix, vagina and external genital organs. Despite the role and importance of cytology in detecting cervical cancer, colposcopy allowed accurate diagnosis in women with abnormal cytology results [9, 12, 23].

Histological verification by biopsy was called the “golden standard” in the diagnosis of HPV-associated diseases. In order to assess and choose the proper treatment, each pathology had to be histologically verified [20].

The objective of this study was to present the opportunity of the conventional PAP smear diagnosis of HPV-associated precancerous and cancerous diseases of the cervix.

MATERIALS AND METHODS

During the period 2019-2021, a retrospective study was carried out covering 128 female patients from Hinkomed MC EOOD and Sv. Marina UMPHAT LTD., Pleven.

The obtained data were processed with MS Office Excel 2019 software.

RESULTS

The study included 128 female patients aged between 16 and 73 years. They were divided into 4 age groups: 16-25 years, 26-45 years, 46-65 years and 66-73 years. The highest ratio of patients belonged to the age group 26-45 years – 64.0% (82 females). The data for the age distribution of the patients included in the study was presented graphically in Fig. 1.

The included patients were divided into three groups according to the PAP test results.

- **The first group** consisted of the patients with PAP I-II results or these were the cytologically not signaled cases. In this group, 74 females were assigned, or 57.8% of those covered.
- **The second group** consisted of patients with PAP results IIIa and higher (IIIb, IV and V). This group included 54 women (42.2% of those covered).

The distribution of the examined persons per groups was presented graphically in Fig. 2

Results in the first group of female patients (cytologically not signaled)

The group consisted of women with PAP I-II result of conventional cytology. The result was interpreted as normal cytology for childbearing and sexually active women. Despite the normal smear group, all patients underwent colposcopic examination of the cervix.

From the patients in this group 31.1% (23 female) had proven HPV infection and a normal colposcopic image. Therefore, the PAP results of these patients were interpreted as true negative and they were excluded from the study.

In the remaining 68.9% (51 female), the colposcopic finding was abnormal or atypical (Fig. 2).

For the patients with abnormal or atypical colposcopic findings (51 women) the next method for diagnostic clarification was applied, namely taking sample for histological examination (biopsy). The histological results were distributed as follows:

- ✓ Cervicitis was found in 13 patients (25.5% at n = 51);
- ✓ CIN I in 26 patients (51.0%, at n = 51);
- ✓ CIN II in 11 patients (51.0%, at n = 51);
- ✓ CRC in 1 patient (2.0%, at n = 51).

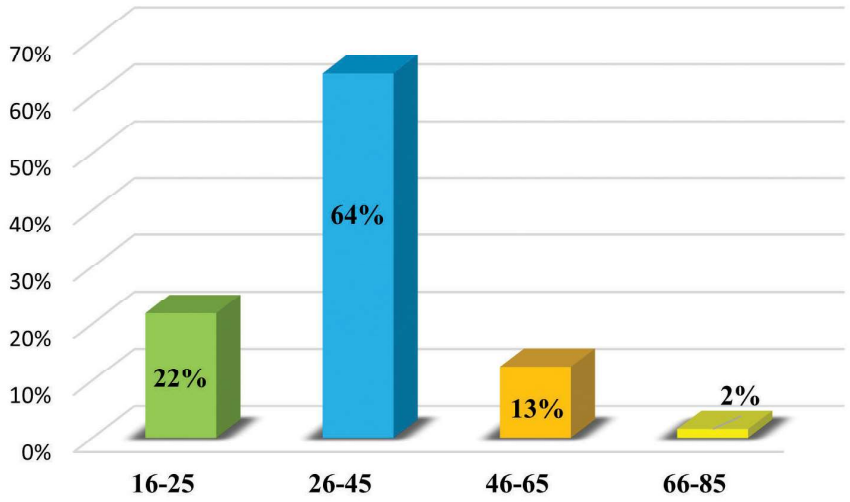

Fig. 1. Age distribution of the female participants in the study

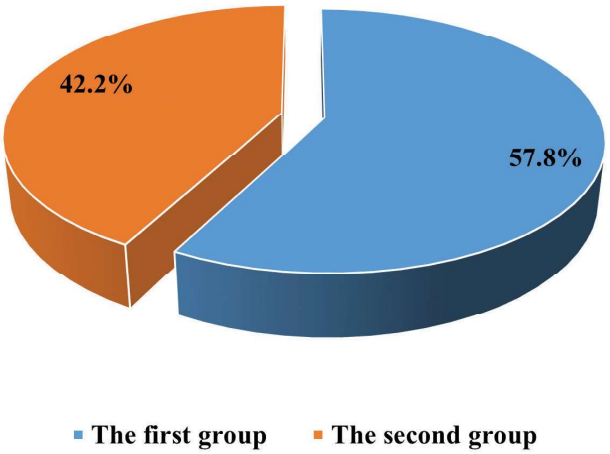

Fig. 2. Percentage distribution of female patients per groups

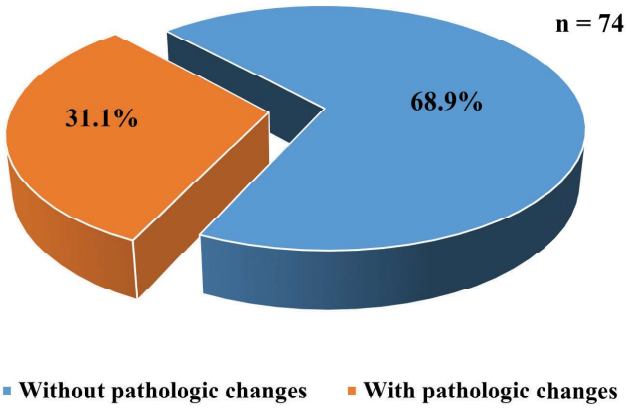

Fig. 3. Distribution of the patients according to the presence or absence of pathology

Results in the second group of patients (cytologically signaled)

The results obtained from the conventional PAP smear were interpreted as abnormal. These were PAP IIIa and a higher group. With such cytodiagnostic results, the basic rule was to undertake additional diagnostic steps. With a view of this recommendation, all patients in this group underwent colposcopy. The test was carried out using a 3% solution of acetic acid. The obtained results of the non-invasive examination proved an atypical colposcopic finding in all patients, which were interpreted as the presence of HPV. Given the colposcopic finding, it was necessary a full range of diagnostic procedures to be performed in order to initiate and follow the proper treatment plan. Therefore, all patients in the group underwent histological verification, by means of a pinch biopsy of the atypical areas.

To interpret the results obtained from the histological sample, a comparison was made between the histological result and that of the PAP test. In this regard, the female patients were divided into two subgroups: those in whom no koilocytes were detected from the smear and those with the presence of koilocytes.

The obtained histological diagnoses of the female patients with the presence of koilocytes from the smear were the following:

- ✓ CIN III in 34 female patients (63.0%, n = 54);
- ✓ Ca colli uteri in situ in 5 female patients (9.3%, n = 54);
- ✓ CRC in 7 female patients (13.0%, n = 54).

The histological results of the female from the subgroup without koilocytes from the PAP smear, were as follows:

- ✓ CIN III in 5 female patients (9,%, n =54);
- ✓ Ca colli uteri in situ in 2 female patients (3.7%, n = 54);
- ✓ CRC in 1 female patients (1.9%, n = 54).

The total distribution of the patients per diagnosis was the following (fig. 4):

- ✓ CIN III in 39 female patients (72.2%, n = 54);
- ✓ Ca colli uteri in situ in 7 female patients (13.0%, n = 54);
- ✓ CRC in 8 female patients (14.8%, n = 54).

DISCUSSION

The analysis of the obtained results proved that the PAP-test was related with the screening of the most common HPV-associated disease, namely, cervical carcinoma. Simultaneously, it was demonstrated that the method was insufficient for early diagnosis of precancerous and cancerous diseases.

The results for the first group of patients (cytologically not signaled) showed that the PAP test alone could not be used as a diagnostic procedure. The study revealed that HPV was histologically verified in 38 female with a normal PAP group. That evidenced that these female patients had false negative smear results, leading to lack of early detection of cervical carcinoma. Patients whose histological results proved cervicitis (25.5%, n = 51) were considered false positives. That was in support of our assertion that the conventional smear was not a sufficient diagnostic method.

The histological verification of CRC, in one of the patients with a normal smear group (from the first group), was alarming. In this case, it was assumed that there

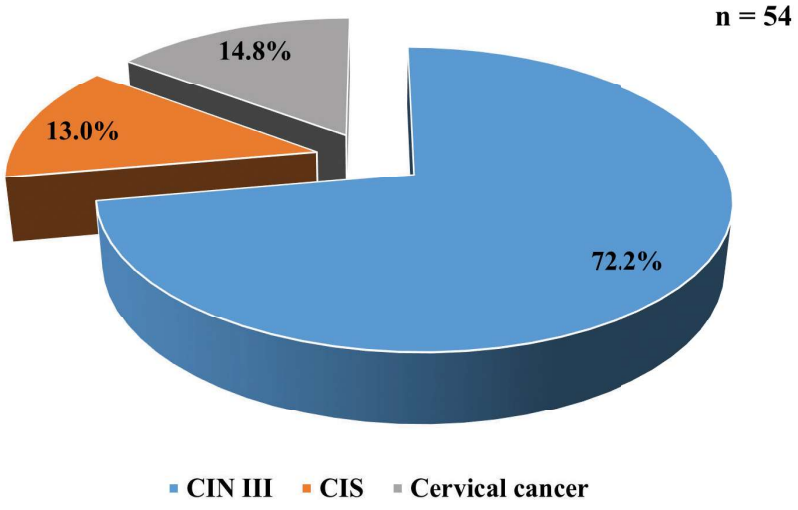

Fig. 4. Distribution of the patients per histological diagnosis

was a false negative PAP result, and we would even say that a mistake had been made. This case cast doubt on the conventional PAP smear sensitivity in the diagnosis of CRC. The data supported the 2000 Cervical Cancer Screening and Management Consensus Conference Report, published by Miller et al. [22].

The results of the second group of female patients (cytologically signaled) showed:

- ✓ 32 of the patients with CIN III and the presence of PAP smear koilocytes were true positive results, and 2 were false positive;
- ✓ 2 of the patients with CIN III without the presence of PAP smear koilocytes were true negative, and 3 were false negative;
- ✓ the presence of HPV was confirmed in 5 of the patients with CIS (and the presence of PAP smear koilocytes);
- ✓ 2 of the patients with CIS (without PAP smear koilocytes) were true negative;
- ✓ 1 of the cases with CRC (without PAP smear koilocytes) was true negative;
- ✓ The presence of the virus was confirmed in 7 of the patients with CRC and with HPV data from the PAP test.

In addition to the low susceptibility of the test, the results obtained in both groups of female patients showed that there were also frequent false-negative results, which, if no other diagnostic method was used, would lead to a wrong diagnosis and a delay in treatment [19]. The study proved that the PAP test was insufficient in 40.95% of the cases when it was used to detect HPV. The results analysis evidenced that the conventional PAP smear was applicable in the detection of HPV infection. These claims correlated with the findings by Kim et al. that a high false positive rate led to misdiagnosis in female patients with CRC [14].

Referring the conventional cytology low susceptibility, Khakwani M. et al. came to the conclusion that liquid-based cytology had a higher susceptibility and adequacy. The assertions thus made correlated with our results [14].

In 2023, Pulkkinen J. et al. published a study demonstrating that there was no specific cytomorphological feature that did not require confirmation by histological refinement. The data obtained by the researchers' team supported our assertion that cytological results alone could not be trusted for a definitive diagnosis [26].

The use of a complex of diagnostic methods improved the accuracy of diagnosis and the timely treatment [6, 23]. This statement was in support of the data analyzed by us, which showed that the combination of PAP with colposcopy and targeted biopsy had an indicative ratio of 43.8%.

The study by Kabaca et al. was also in confirmation of our results. The researchers carried out a study among 201 female patients. Analyzing the obtained data, it was proven that only 27.6% (24 female) of the patients with normal cytological test results (PAP test) had negative HPV tests [12].

In 2024, Dura MC et al. conducted a retrospective cohort study analyzing the medical records of over 10,000 female patients. Through the analysis of the results, it was proven that the efficiency only of the PAP smear was lower compared to that of the HPV DNA test. At the same time, the authors ascertained that the susceptibility of a joint DNA and cytological test was several times higher, in comparison with the independent ones. Despite the analysis, they emphasized that the cytological test had a higher specificity than the DNA test. The reviewed results confirmed our statement that the PAP test had a low diagnostic value for HPV-associated diseases [9].

In the comprehensive textbook and atlas Colposcopy published by Springer, and specifically in the chapter "The Importance of Cytology, Biopsy, and HPV Testing" the authors described cytology as the "gold standard" in cervical carcinoma screening. However, the authors pointed out that conventional Pap smear did not provide a reliable diagnosis, which supported the results obtained from our study [18].

In contrast to the low susceptibility and diagnostic value of the conventional PAP smear, which we had proven, was the study of Kaya Terzi N. et al. The authors concluded that PAP had remained a reliable method for cervical pathology diagnosing. However, the need to introduce DNA tests for HPV in all cytological studies was also emphasized. That conclusion of the authors' team supported our assertion that the conventional PAP smear could not be used as a stand-alone method for the diagnosis of HPV-associated diseases [14].

CONCLUSION

PAP test had been insufficient for the diagnosis of HPV-associated precancerous and/or cancerous diseases of the cervix. Conventional PAP smears were sufficient in the past, but now they are morally outdated. In this regard, it would be required to use PAP in conjunction with at least one other diagnostic method. The recommendations of the world gynecological and oncological associations had been that conventional cytodiagnostics of the cervix should be performed in conjunction with at least colposcopy and HPV DNA typing.

The properly organized and timely screening, among female of reproductive age, would allow early diagnosis, and appropriate treatment at the right time. That might reduce the morbidity, complications and mortality rates caused by carcinoma of the cervix. Access to high-tech diagnostic methods has been the right of every female advocated in the WHO Global Strategy to Eliminate Cancer, and our study proved the need for their implementation.

Conflict of Interest: *The authors declare no conflicts of interest related to this work.*

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Ethical statement: *This study has been performed in accordance with the ethical standards as laid down in the Declaration of Helsinki.*

Informed Consent from Participants: *Informed consent was obtained from all participants included in the study.*

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