ORIGINAL CONTRIBUTION

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INTERPLAY OF EPIGENETIC REGULATION OF KI-67 AND P53 BY MIR-21 AND MIR-34A IN CERVICAL INTRAEPITHELIAL NEOPLASIA

Background. Cervical cancer (CC), primarily linked to persistent HPV infection, arises from complex genetic and epigenetic alterations. The early detection of cervical intraepithelial neoplasia (CIN) allows for CC prevention. Recent data highlights the importance of epigenetic biomarkers, including non-coding RNAs such as miR-21 and miR-34a. Our **aim** was to investigate the interplay between Ki-67 and p53 expression and their epigenetic regulation by miR-21 and miR-34a to better predict the course of CIN. **Materials and Methods.** Tumor biopsies from 50 patients with CIN 1–3/HSIL were analyzed. We performed immunohistochemical analysis of Ki-67 and p53 expression and qRT-PCR for the analysis of miRNA expression. **Results.** The average miR-21 and miR-34a levels were 5.8 ± 2.8 and 1.42 ± 0.85 (a.u.), respectively, while Ki-67 and p53 averaged 136.9 ± 79.9 and 93.15 ± 49.5 H-score points. Positive correlations were found between miR-21 and Ki-67 (r = 0.76) and miR-34a and p53 expressions (r = 0.65). Tumors with low Ki-67 showed 2.48-fold lower miR-21 levels, and low p53 tumors showed 4.2-fold lower miR-34a levels. While no correlation with age or menstrual status was found, miR-21 (r = 0.78), Ki-67 (r = 0.68), and miR-34a (r = –0.59) correlated with CIN grading ($p < 0.05$). The miR-21 and Ki-67 levels increased in CIN 2 and CIN 3 compared to CIN 1 in both HPV-positive and HPV-negative samples. The miR-34a levels were the lowest in CIN 3 HPV-negative samples and significantly decreased with CIN progression in HPV-positive samples. The p53 levels were significantly higher in CIN 3 cases of both the HPV-positive and HPV-negative groups. **Conclusion.** Our study demonstrates that the miR-21, miR-34a, Ki-67, and p53 expression levels are significantly correlated with each other and are distinctly associated with the progression of CIN grades and HPV status, highlighting their potential as crucial CC biomarkers.

Keywords: miRNA, Ki-67, p53, cervical intraepithelial neoplasia, HPV.

Cervical cancer (CC) represents a significant global health burden. Understanding the molecular underpinnings of this malignancy is paramount for developing effective diagnostic, prognostic, and therapeutic strategies [1]. CC diagnosis, prognosis, and management rely on a suite of molecular bio-

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markers that provide critical insights beyond traditional cytology and histology. It is well known that the CC development is strongly linked to persistent infection with high-risk human papillomaviruses (HPV). Several other biomarkers have been found, for example, p16INK4a and Ki-67 [2]. Scientists continue to identify other potential biomarkers for CC diagnosis, prognosis, and treatment response. These include epigenetic biomarkers, such as DNA methylation and non-coding RNAs (ncRNAs) and circulating DNA (cDNA) [3].

CC develops through a multistep process, starting with HR-HPV infection transforming normal cervical cells into cervical intraepithelial neoplasia (CIN), eventually leading to invasive cancer. While low-grade lesions (CIN I) often resolve, high-grade lesions (CIN II—III) frequently progress. Like other cancers, CC shows abnormal microRNA (miRNA) expression. Specifically, studies have observed decreased miR-34a and increased miR-21-5p in CC, with these changes becoming more pronounced as lesions progress [4]. These miRNA alterations are early-onset events in CC development and are more specific than HPV positivity in differentiating low- from high-grade cervical disorders, suggesting their potential as molecular markers for predicting cervical carcinogenesis.

Earlier, much attention was paid to the p53 status of tumors, and different studies obtained contradicting results for the involvement of p53 aberrant expression in CIN progression [5]. In the last decade, interest in this matter has risen again, due to the development of new therapeutic approaches in cancer treatment [6].

In our research, we focused our attention on the interplay between Ki-67 and p53 expression and their epigenetic regulation in the CIN course. We chose miR-21 and -34a as markers of interest due to their proven involvement in the regulation of the mentioned proteins, as well as a significant role in carcinogenesis [7, 8].

Table 1. **Clinical and pathological characteristics of patients**

	Number of patients	
	n	%
Total number of patients	50	100
Average age, years	39.4 ± 15.79	
Age range	22—79	
Menstrual function preserved	31	62
Menopause	19	38
CIN grade		
CIN 1/HSIL	15	30
CIN 2/HSIL	20	40
CIN 3/HSIL	15	30
HPV status		
HPV-positive	27	54
HPV-negative	23	46

Materials and Methods

Patients. Tissue biopsy samples were obtained from 50 patients diagnosed with CIN 1—3/high-grade squamous intraepithelial lesion of the cervix (HSIL) and suspicion of CC, who were treated at the NPO "National Cancer Institute" and the Medical Center of Colposcopy "LyNa" (Kyiv) over 2020—2024. All patients provided informed consent on the use of their clinical data for scientific purposes. The research was approved by the Medical Ethical Committee of the NPO "National Cancer Institute" and was carried out in conformity with the guidelines of the Declaration of Helsinki. Before the study, all patients did not receive treatment and were examined using conventional clinical and laboratory methods according to the standards of diagnosis and treatment of cancer patients approved by Order No. 554 of 17.09.2007 of the Ministry of Health of Ukraine. The final diagnosis and HPV status were established using immunohistochemical (IHC) analysis according to Standard of Medical Care "Cervical Cancer Screening. Management of patients with abnormal screening results and precancerous conditions of the cervix" (Order of the Ministry of Health of Ukraine dated June 18, 2024, No. 1057). Tissue samples were encoded and depersonalized. The general clinical characteristics of the patients are presented in Table 1.

Immunohistochemical study. The study of the Ki-67 and p53 expression in biopsy tissue was performed on 5-μm thick paraffin sections using monoclonal antibodies (clone MIB-1 DakoCytomation, Denmark, and clone DO-7, Thermo Scientific, USA, respectively). A Master Polymer Plus Detection System (Peroxidase) reagent kit (Incl. DAB Chromogen) (Master Diagnostica, Spain) was used to visualize the reaction results following the

manufacturer's recommendations. The sections were stained with Meyer's hematoxylin (Thermo Scientific Richard-Allan, USA). Results were assessed as described earlier [9].

Real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR). Total RNA from tumor tissue was isolated using a commercial kit RNeasy FFPE Kit (QIAGEN, Germany), according to the manufacturer's recommendations. The quantity of isolated RNA was determined using a "NanoDrop 2000c" spectrophotometer (Thermo Scientific, USA). The purity of the isolated RNA was monitored by the ratio of the optical absorption values at the 260 and 280 nm wavelengths. RNA was dissolved in Tris-EDTA buffer and stored at –20 °C until use. The RT-PCR was performed on a quantitative detection system QuantStudio 5 Dx Real-Time PCR System (Thermo Fisher Scientific, USA), using a commercial kit for RT-PCR TaqMan MicroRNA Assay (Thermo Fisher Scientific, USA) according to the manufacturer's protocol.

The primer sequences for the detection of miRNA-21 and -34a were obtained using the resource genomics.dote.hu:8080/mirnadesigntool/ and synthesized by Metabion, Germany. RNU48 microRNA was used as an endogenous control to objectify expression parameters. The relative expression of miR-21 and -34a was determined by the comparative ΔCT method described earlier [10].

Statistical methods. Statistical processing of the obtained results was carried out using STATISTICA 6.0 program (Statistica Inc., USA). Standard descriptive, parametric, and non-parametric statistical methods were used. A comparison of the reliability of differences between the mean values was carried out using Student's *t*-test (for a parametric distribution) or the Mann — Whitney U-test (for a non-parametric distribution). The data are presented as M ± m, where M is the arithmetic mean; m is the standard error of the mean, or as a percentage for relative values. The differences at $p \leq 0.05$ were considered significant.

Results and Discussion

We analyzed the expression of miR-21 and -34a as well as Ki-67 and p53 proteins in biopsy samples from 50 CIN patients. In the total group, the average miR-21 and -34a levels yielded 5.8 ± 2.8 and 1.42 ± 0.85, respectively, while average Ki-67 and p53 expressions were136.9 ± 79.9 and 93.15 ± 49.5 H-score points, respectively. We found a positive correlation between miR-21 and Ki-67 (r = 0.76) and miR-34a and p53 (r = 0.65) in tumor tissue of the studied CIN patients (Fig. 1).

We divided the patients into groups with high and low Ki-67 and p53 expressions and estimated differences in the miR-21 and -34a levels. As can be seen from Fig. 2, in tumors with low Ki-67 expression, miR-21 expression was 2.48 times lower than that in high-Ki-67-expressing cohort. Similarly, in tumors with low p53 expression, miR-34a expression was 4.2 times lower compared to the group with high p53 expression levels.

No association of the miR-21, -34a, Ki-67, and p53 levels with the age and menstrual status of CIN patients was found.

We established that the progression of CIN grading was associated with the expression patterns of miR-21, miR-34a, Ki-67, and p53. The miR-21 and Ki-67 levels positively correlated with CIN grading, and the miR-34a levels negatively correlated with CIN grading (r = 0.78, 0.68, and –0.59, respectively) ($p < 0.05$). This coincided with the literature data on the progressive upregulation of miR-21 alongside the increasing grade of the lesion from

Table 2. **Primers used in this study**

Primer	Sequence 5'—3'
miR-21-5p-RT	GTTGGCTCTGGTGCAGGGTCCGA GGTATTCGCACCAGAGCCAAC TCAACA
miR-21-5p-F	GTTTGGTAGCTTATCAGACTGA
miRNA-34a-5p-RT	GTTGGCTCTGGTGCAGGGTCCGA GGTATTCGCACCAGAGCCAAC ACAACC
miRNA-34a-5p-F	GTGTGGCAGTGTCTTAGCT
Universal Reverse primer	GTGCAGGGTCCGAGGT
RNU48-R	CTGCGGTGATGGCATCAG
RNU48-F	AGTGATGATGACCCCAGGTAACTC

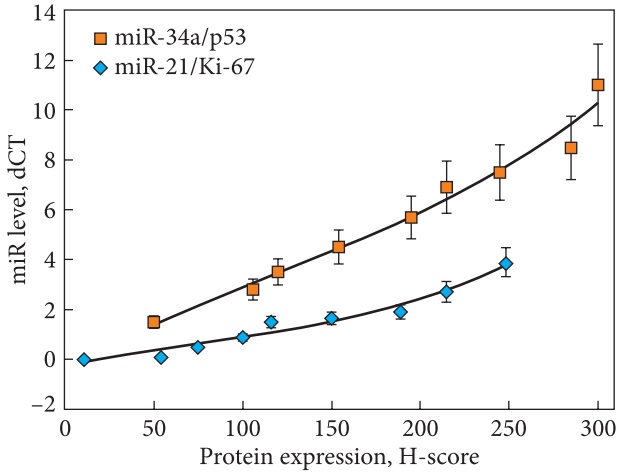

Fig. 1. miR-21 vs. Ki-67 and miR-34a vs. p53 correlations in tumor tissue of studied CIN patients

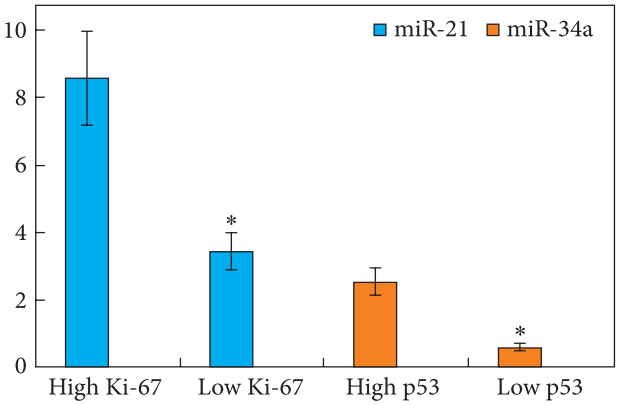

Fig. 2. Expression of miR-21 and miR-34a depending on the Ki-67 and p53 levels in CIN samples. *$p < 0.05$ compared to the group with a high expression of the studied protein

low-grade to high-grade CIN and ultimately to invasive carcinoma [11]. Conversely, miR-34a expression generally demonstrated a significant downregulation with increasing CIN grade, particularly in high-grade lesions and invasive cancer, indicating a compromised tumor suppressive pathway [12]. Other authors reported similar data [4].

The Ki-67 proliferation index escalates from low-grade to high-grade CIN and invasive cancer, as the proportion of actively dividing cells markedly increases in more severe dysplastic and malignant states [13]. The status of p53 also shifts; while normal or low-grade CIN might show a wild-type p53 function, aberrant p53 expression (often characterized by nuclear accumulation due to mutation or stabilization, or conversely, complete loss of expression) becomes more prevalent in high-grade CIN and invasive CC, signifying the disruption of a crucial tumor suppressor pathway in advanced disease. However, similarly to Funk et al. [14], we did not find any significant correlation.

The tumor suppressor p53 activates miR-34a expression, which, in turn, mediates some of the pro-apoptotic effects of p53 [15]. Oncogenic HPV infection, specifically through the E6 oncoprotein, disrupts this pathway by reducing p53 and, consequently, the miR-34a levels. This reduction in miR-34a is associated with a high-risk HPV infection via a p53-dependent mechanism [16].

Therefore, we compared miR-21, -34a, Ki-67, and p53 expression in HPV-positive and HPV-negative samples and found that the miR-21 and miR-34a levels are 1.33 and 1.37 times higher in HPV-positive cohort. As seen in Fig. 3, *a,* the levels of miR-21 were lower in HPV-negative samples. Nevertheless, its expression was higher in CIN 2 and CIN 3 cohorts compared to CIN 1 in both HPV-positive (by 1.94 and 2.42 times, respectively) and HPV-negative samples (by 2.55 and 3.43 times, respectively). Similarly, the levels of Ki-67 were higher in the CIN 2 and CIN 3 cohorts by 2.07 and 2.33 times in the HPV-positive samples and 2.03 and 2.29 times in the HPV-negative samples, respectively (Fig. 3, *b)*.

The miR-34a levels in CIN 1 HPV-positive samples were 1.86 times lower than in CIN 1 HPV-negative samples (Fig. 3, *c)*. Also, in the CIN 3 patients, these levels were 2.1 and 4.66 times lower compared to CIN 1 and CIN 2 in HPV-positive samples. In the\CIN 3 cohort of HPV-negative samples, its levels were the lowest ($p < 0.05$).

For p53 protein, significant differences were established in the CIN 3 cohort in both HPV-positive and HPV-negative groups compared to the CIN 1 samples (by 1.89 and 1.88 times, respectively) and CIN 2 samples (by 2.1 and 1.89 times, respectively) (Fig. 3, *d)*

The functions of miR-21, as a regulator of cancer progression, play a crucial role in promoting angiogenesis, invasion, and metastasis in tumors. miR-21 is frequently overexpressed in various types of cancer and benign tumors and is believed to contribute to the cancer development [17]. According to Yao and Lin [18], miR-21 expression is elevated in CC patients with HPV infection, implying that HPV may promote cancer formation by altering the expression of oncogenic microRNAs. This suggests that miR-21 may act as an oncogene in CC, with the hpv16 E6 and E7 oncoproteins playing a role in this mechanism. In the study by Liu et al. [19],

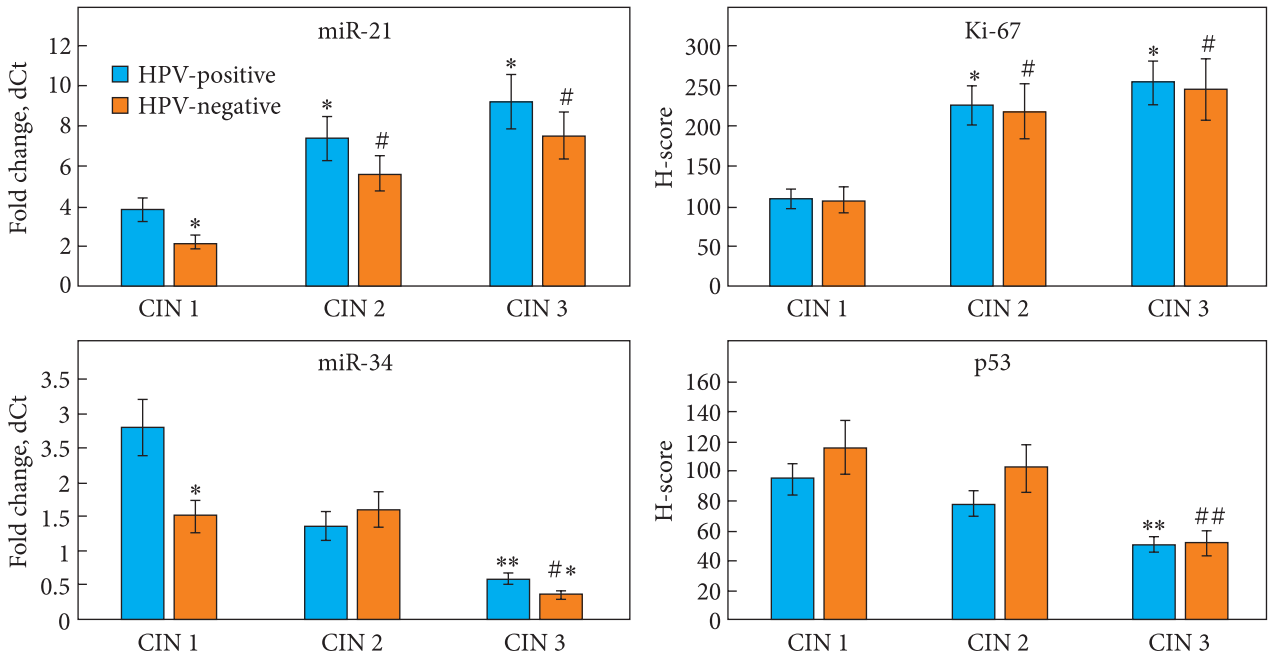

Fig. 3. Levels of miR-21, miR-34a, Ki-67, and p53 in cervical tumor tissues stratified by HPV status and CIN grade. * $p < 0.05$ compared to CIN 1 HPV-positive samples; # $p < 0.05$ compared to CIN 1 HPV-negative sample; ** $p < 0.05$ compared to CIN 1 and CIN 2 HPV- positive samples; #* $p < 0.05$ compared to CIN 1, CIN 2, CIN 3 HPV-positive and CIN 1 and CIN 2 HPV-negative samples; ## $p < 0.05$ compared to CIN 1 and CIN 2 HPV-positive and HPV-negative samples

miR-21 was also found to be upregulated in HPV-positive CC, mirroring our findings, though the observed increase was insignificant.

Also, Bumrungthai et al. [20] demonstrated that miR-21 is associated with HPV infection and is involved in cervical lesions as well as cervicitis, and its up-regulation in tumor-stroma might be involved in the inflammation process and CC progression. In contrast, miR-21 expression was reduced in HPV-positive samples.

miR-34a was significantly upregulated in HPV-positive CC compared to HPV-negative healthy individuals and HPV-positive CIN [21]. Gocze et al. [22] reported that the miR-34a levels were significantly reduced in CIN2-3 compared to CIN1 and further decreased in SCC compared to CIN2-3 ($p = 0.021$). We also found significant alterations in miR-21 ($p = 0.002$) and miR-34a ($p = 0.001$) expression in SCC/CIN2-3. Downregulation of miR-34a was significantly associated with HPV 16 positivity (CIN2-3 vs. CIN1: $p = 0.027$; SCC vs. CIN2-3: $p = 0.036$). Additionally, miR-34a expression was significantly influenced by both the smoking status and the presence of HPV 16.

Significantly reduced miR-34a expression is observed not only in CC but also in precancerous lesions, with the lower levels in CIN2—3 compared to CIN1. Some studies also report reduced miR-34a in HPV-positive cervical tissues, although conflicting reports suggest an increase in HPV-associated cancer. The HPV E6-mediated suppression of miR-34a is likely to be an early event in the CC development [23].

The expression patterns of both Ki-67 and p53 exhibit distinct correlations with the progression of cervical lesions, from normal epithelium through different grades of CIN up to invasive carcinoma. The Ki-67 proliferation index dramatically escalates from low-grade to high-grade CIN and invasive cancer, indicating a marked increase in actively dividing cells as the disease progresses [24]. While p53 protein levels might vary, aberrant p53 expression (often characterized by nuclear accumulation due to mutation or stabilization, or conversely, complete loss of expression) becomes more prevalent in high-grade CIN and invasive CC, signifying the disruption of a crucial tumor suppressor pathway in the advanced disease [25].

The combined assessment of Ki-67 and p53, alongside miR-21 and -34a, provides valuable insights into the aggressiveness and progression of

cervical lesions, serving as important molecular indicators [13]. Elevated Ki-67 levels, coupled with aberrant p53 expression, can collectively signal a more aggressive form of the disease, potentially predicting a poorer response to conventional therapies and guiding the selection of more intensive or novel targeted interventions [24]. This integrated molecular profile offers a more specific and sensitive approach to identifying individuals with a high risk of progression to CC, thereby supporting timely intervention and improving clinical outcomes.

This study is crucial for unraveling complex molecular mechanisms driving CIN progression. By elucidating the distinct roles and correlations of miR-21, miR-34a, Ki-67, and p53, it significantly enhances our understanding of the disease's pathogenesis. The findings provide critical insights into developing more precise diagnostic and prognostic tools for early detection and risk stratification.

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ВЗАЄМОДІЯ ЕПІГЕНЕТИЧНОЇ РЕГУЛЯЦІЇ KI-67 ТА P53 ЗА ДОПОМОГОЮ MIR-21 ТА MIR-34A ПРИ ПРОГРЕСІЇ ДИСПЛАЗІЇ ШИЙКИ МАТКИ

Стан питання. Рак шийки матки є глобальною проблемою в онкології і пов'язаний головним чином зі стійкою ВПЛ-інфекцією. Він виникає внаслідок складних генетичних та епігенетичних змін, проте його розвитку можна запобігти, якщо вчасно виявити диспластичні процеси в цервікальному каналі на ранній стадії. Ефективна діагностика та лікування цього злоякісного новоутворення залежать від розуміння його молекулярних основ. Нещодавні дані підкреслюють важливість епігенетичних біомаркерів, включаючи некодувальні РНК, такі як miR-21 та miR-34a. **Мета.** Дослідити взаємодію між експресією Ki-67 та p53 та їх епігенетичною регуляцією через miR-21 та miR-34a для кращого прогнозування перебігу дисплазії шийки матки. **Матеріали та методи.** Дослідження рівнів miR-21, miR-34a, Ki-67 та p53 проводили в біоптатах пухлин 50 пацієнток з дисплазією шийки матки (CIN 1–3/HSIL). Експресію Ki-67 та p53 визначали імуногістохімічним методом, рівні miR-21 та miR-34a — методом ПЛР у реальному часі. **Результати.** Середні рівні miR-21 та miR-34a становили 5,8 ± 2,8 та 1,42 ± 0,85 відповідно, тоді як Ki-67 та p53 становили в середньому 136,9 ± 79,9 та 93,15 ± 49,5 балів за шкалою H-score. Виявлено позитивну кореляцію між miR-21 та Ki-67 (r = 0,76) та miR-34a та p53 (r = 0,65). Зразки з низьким Ki-67 показали в 2,48 рази нижчий рівень miR-21, а зразки з низьким рівнем p53 мали в 4,2 рази нижчий рівень miR-34a. Хоча кореляції з віком чи менструальним статусом не було виявлено, miR-21 (r = 0,78), Ki-67 (r = 0,68) позитивно, а miR-34a (r = –0,59) негативно корелювали зі ступенем дисплазії ($p < 0,05$). Рівні miR-21 та Ki-67 збільшилися в CIN 2 та CIN 3 порівняно з CIN 1 як у ВПЛ-позитивних, так і у ВПЛ-негативних зразках. Рівні miR-34a були найнижчими в ВПЛ-негативних зразках із CIN 3 та значно знижувалися з прогресуванням CIN у ВПЛ-позитивних зразках. Рівні p53 були значно вищими в CIN 3 як у ВПЛ-позитивних, так і в ВПЛ-негативних хворих. **Висновок.** Наше дослідження демонструє, що рівні експресії miR-21, miR-34a, Ki-67 та p53 суттєво корелюють один з одним та чітко пов'язані з прогресуванням дисплазії шийки матки, а також зі статусом ВПЛ, що підкреслює їхній потенціал як перспективних біомаркерів.

Ключові слова: мікроРНК, Ki-67, дисплазія шийки матки, ВПЛ.