International Journal of Medical Sciences And Clinical Research

VOLUME Vol.05 Issue10 2025
PAGE NO. 29-30
DOI 10.37547/ijmscr/Volume05Issue10-06

Analysis Of Epigenetic Changes In Cervical Dysplasia Associated With Human Papillomavirus (HPV)

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Received: 19 August 2025; **Accepted:** 15 September 2025; **Published:** 17 October 2025

Abstract: The aim of this review is to analyze the epigenetic mechanisms involved in the development of cervical intraepithelial neoplasia (CIN) associated with human papillomavirus (HPV) infection and to evaluate the prognostic potential of DNA methylation as a biomarker of precancerous cervical lesions. The review summarizes recent international studies (2010–2024) on DNA methylation of CADM1, MAL, FAM19A4, PAX1, and miR124-2 genes and their roles in epithelial transformation. The perspectives of implementing epigenetic testing in clinical screening and diagnosis of precancerous cervical conditions are also discussed.

Keywords: Cervical dysplasia, human papillomavirus, DNA methylation, epigenetics, biomarkers, cervical cancer.

Introduction: Cervical dysplasia (cervical intraepithelial neoplasia — CIN) is a precancerous condition that develops against the background of persistent human papillomavirus (HPV) infection. According to the World Health Organization (WHO), more than 600,000 new cases of cervical cancer are diagnosed annually worldwide, and over 90% of them are associated with oncogenic HPV types, predominantly types 16 and 18.

However, the presence of HPV infection does not always lead to invasive cancer. Only a fraction of infected women develop epigenetic and genetic alterations that trigger malignant transformation of the epithelium. This explains the growing interest in studying epigenetic mechanisms that regulate the expression of oncogenes and tumor suppressor genes.

1. Epigenetic Mechanisms of Cervical Carcinogenesis

Epigenetics encompasses processes that affect gene activity without altering the DNA sequence itself. The main forms of epigenetic regulation include:

- DNA methylation — the addition of methyl groups to cytosine residues within CpG islands, leading to gene silencing;
- Histone modifications — acetylation, methylation, and phosphorylation that alter chromatin accessibility;
- MicroRNA regulation — post-transcriptional control of gene expression.

In the context of HPV-induced dysplasia, hypermethylation of tumor suppressor genes is particularly significant, as it leads to the inactivation of apoptosis and differentiation mechanisms.

2. DNA Methylation and Progression of Cervical Dysplasia

Numerous studies confirm that the degree of DNA methylation increases proportionally to the severity of CIN. Lai et al. (2010) were the first to demonstrate that hypermethylation of the PAX1 and SOX1 genes is associated with progression from CIN I to CIN II/III.

Steenbergen et al. (2014) and Verhoef et al. (2014) showed that methylation of FAM19A4 and miR124-2 is significantly elevated in CIN III and invasive cervical cancer, with diagnostic AUC values exceeding 0.85. El-Zein et al. (BMC Cancer, 2023) conducted clinical validation of new markers (FAM19A4, CADM1, MAL) and confirmed their prognostic value for CIN II+. The combination of FAM19A4 and miR124-2 methylation demonstrated a sensitivity of 84% and a specificity of 78% for detecting CIN2+.

These findings indicate that epigenetic testing can be used not only for diagnosis but also for predicting the progression of precancerous lesions.

3. MicroRNAs and Histone Modifications in Epithelial Transformation

In addition to DNA methylation, epigenetic remodeling also involves changes in microRNA profiles and chromatin structure.

Decreased expression of miR-34a and miR-203 correlates with activation of viral oncogenes E6/E7 and loss of apoptotic control.

Elevated miR-21 levels promote tumor cell proliferation and invasion.

According to Zhang et al. (2021), hyperacetylation of H3K9 and hypermethylation of H3K27 enhance the expression of oncogenic signaling pathways such as PI3K/AKT and Wnt/β-catenin.

These mechanisms establish a stable epigenetic profile that promotes malignant transformation of cervical epithelial cells.

4. Clinical Significance of Epigenetic Markers

Incorporation of epigenetic assays into HPV screening algorithms significantly improves diagnostic accuracy. Epigenetic panels (PAX1/SOX1, FAM19A4/miR124-2, CADM1/MAL) are currently undergoing clinical trials in the Netherlands, the United Kingdom, and Taiwan.

Their main advantages include:

1. Risk stratification of HPV-positive women for CIN2+ progression;

2. Reduction in the number of unnecessary biopsies;

3. Independence from the subjectivity of cytological evaluation;

4. Potential for automation and standardization of laboratory testing.

Thus, epigenetic testing may serve as an effective complement to standard cytology and HPV testing.

5. Prospects for Clinical Implementation of Epigenetic Analysis

In the near future, integration of methylation analysis into national cervical screening programs is expected.

Modern qPCR and NGS platforms allow simultaneous quantification of methylation levels in dozens of genes, facilitating the development of multigene epigenetic panels.

Additionally, liquid biopsy — the detection of methylated DNA in cervical secretions or blood plasma — is being actively studied as a noninvasive and highly accurate diagnostic approach.

CONCLUSION

Epigenetic alterations play a key role in the pathogenesis of HPV-associated cervical dysplasia.

Methylation of genes such as CADM1, MAL, FAM19A4, PAX1, and miR124-2 reflects the degree of neoplastic transformation and may serve as a highly sensitive biomarker for early diagnosis and prognosis of cervical cancer.

The introduction of epigenetic testing into clinical practice will help to personalize screening, increase its sensitivity, and reduce the number of invasive procedures. Future research should focus on standardizing methylation-specific PCR methodologies and defining clinically relevant methylation thresholds for practical use.

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