AJCMI
Avicenna Journal of Clinical Microbiology and Infection
Avicenna J Clin Microbiol Infect. 2025;12(2):91-98. doi:10.34172/ajcmi.3589
http://ajcmi.umsha.ac.ir
UMSHA Press

Review Article

Human Papillomavirus, Deregulated Micro Ribonucleic Acids, and Long Non-coding Ribonucleic Acids in Cervical Cancer Patients: A Review Study

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Article history:
Received: December 9, 2024
Revised: January 22, 2025
Accepted: January 26, 2025
ePublished: June 30, 2025

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Abstract
Cervical cancer (CC) ranks fourth in incidence and is one of the most serious global health problems. Infection with high-risk human papillomaviruses (hrHPV), including types 16 and 18, plays a significant role in the occurrence of this type of cancer. Micro ribonucleic acids (miRNAs) and long non-coding RNAs (lncRNAs) are essential in various cellular processes. The effect of changes in the expression of these oligonucleotides on carcinogenesis has been confirmed in many research studies. Therefore, investigating the differential expression of miRNAs and lncRNAs in cancer biology is a useful method for early detection of precancerous lesions. This research aimed to review the current knowledge on the correlation between HPV infections, dysregulation of miRNAs, and lncRNAs in CC patients. The required data were searched and collected by entering relevant keywords in scientific databases, such as the National Center for Biotechnology Information, ScienceDirect, EMBASE, Scopus, and Google Scholar. Articles related to HPV infections, dysregulation of miRNAs, and lncRNAs in CC were selected for review and study. Based on our findings, various alterations and deregulation of expression profiles in miRNAs and lncRNAs by comparing healthy people and patients were reported regarding CC. Furthermore, it was found that persistent infection with HPV affects miRNA and lncRNA expression patterns. E6 and E7 oncoproteins of HPV are the two main proteins in cervical carcinogenesis. This search highlighted 43 deregulated miRNAs and 37 deregulated lncRNAs. By further analyzing and identifying the exact mechanism of function and the relationship between HPV oncoproteins and the expression changes, it is possible to achieve great goals in the field of early diagnosis and treatment of CC.
Keywords: Human papillomavirus viruses, MiRNAs, Cervical cancer, Oncoprotein, LncRNAs

Please cite this article as follows: Asadzadeh A, Abbasi M, Behboodian B, Askari MJ. Human papillomavirus, deregulated micro ribonucleic acids, and long non-coding ribonucleic acids in cervical cancer patients: a review study. Avicenna J Clin Microbiol Infect. 2025;12(2):91-98. doi:10.34172/ajcmi.3589

Introduction

Cancer ranks second as one of the most common causes of death, which has increased significantly recently (1). Uncontrolled cell division can occur in various tissues. Studying multiple cancers in females has shown that cervical cancer (CC) ranks fourth with high prevalence. This type of cancer is preceded by breast, colorectal, and lung cancer. Two main subtypes of cervical carcinoma have been classified based on the location of changes in squamous or glandular cells of the cervix. Squamous cell carcinoma (SCC) and adenocarcinoma are considered the most common type and the less common type, respectively (2,3). Current treatments for early-stage CC, advanced disease, and recurrent CC include concurrent chemoradiation, neoadjuvant chemotherapy before surgery and radiation, single-agent treatment, combination treatment, and platinum- and non-platinum-based therapy (4).

The human papillomavirus (HPV) has a significant impact on global health. HPV is responsible for cancer in various tissues, such as the cervix, anus, penis, vulva, vagina, and oropharynx. Untreated infection with HPV has been reported as the main cause of CC. There are over 500 000 new cases and 280 000 deaths from CC every

year (5,6). This epitheliotropic virus belongs to the family *Papillomaviridae*. Based on the pathogenicity of HPV, viruses are classified into low-risk (lrHPV) and high-risk (hrHPV) categories. The possibility of HPV infection in HIV-positive people with a weak immune system is high, and some sexual behaviors, such as the presence of more sex partners, infrequent use of condoms, and multiple pregnancies, are other effective parameters in increasing the probability of infection with this virus. Untreated hrHPV, especially HPV16 and HPV18 infections, leads to cell changes in the cervical epithelium that cause it to become precancerous and then cancerous (5,7,8). Prevention strategies for HPV infection include defensive vaccinations, screening, and early detection of individuals with cervical cancerous lesions. Viral oncoproteins change the expression of some regulatory RNAs, promoting the development of intraepithelial lesions. These changes are related to an imbalance in the regulation of other genes and epigenetic modifications. Shutting down various tumor suppressor factors and turning on different tumor-stimulating factors cause neoplastic progression in cervical epithelial cells, which can be used as biomarkers (6,8).

The tiny oligonucleotides known as microRNA (miRNAs) range in length from 19 to 25 nucleotides (9). These types of RNAs are single-stranded molecules and have important biological functions. MiRNAs have important effects on the nucleus by modifying chromatin structure and regulating alternative splicing. They bind to the target mRNA to prevent protein production and sometimes negatively regulate its expression. MiRNA expression changes in response to hormonal alteration, diet, DNA methylation, and various diseases. The deregulated expression of miRNAs can work as either an anti-oncogene factor or a tumor-stimulating factor under different conditions. Therefore, their identification is crucial in the diagnosis and treatment of different types of cancer (9-12).

Longer RNAs with more than 200 nucleotides that cannot be converted into protein are named long non-coding RNAs (lncRNAs). The crucial functions of lncRNAs are associated with regulation at different levels. Furthermore, lncRNAs widely participate in multiple physiological processes and are related to various diseases. Thus, they are used as important biomarkers for the diagnosis of health and disease conditions (12-14).

In addition to their diagnostic applications, miRNAs and lncRNAs have great therapeutic potential in cancer and other diseases due to their role in controlling gene expression, tumor growth, metastasis, and drug resistance (12).

Changes in miRNA and lncRNA expression patterns were identified in the abnormal cells of the cervix. Considering the critical role of molecular biomarkers in the early diagnosis and management of different types of abnormal cells in the cervix, our research seeks to review the correlation between HPV infections, dysregulation of miRNAs, lncRNAs, and CC.

Materials and Methods

International databases were used to obtain the latest articles about HPV infection, miRNAs, and lncRNAs related to cervical carcinoma. English-language publications from the National Center for Biotechnology Information, ScienceDirect, EMBASE, Scopus, Google Scholar, and various other scientific databases were collected and screened. Keywords used for searching included “cervical cancer”, “human papillomavirus”, “oncoproteins”, “squamous cell carcinomas”, “adenocarcinoma”, “long non-coding RNAs”, “Onco-lncRNA”, “HPV16”, “HPV18”, “miRNAs”, “cervical neoplasm”, and “cervical malignant”.

Results and Discussion

Human Papillomavirus Infections and Cervical Cancer

The hereditary material of HPV is double-stranded deoxyribonucleic acid in a circular form and consists of 8000 base pairs. This genome encodes two types of early and late proteins. E1, E2, E4, E5, E6, and E7 are in the early protein category and are responsible for viral replication, transcription, cell cycle control, and oncogenesis. L-1 and L-2 are the two late proteins, which are components of the virion capsid, and have a significant function in the virus transmission process. In addition, the virus genome has a non-coding region that controls replication and transcription processes (5,8). Harold Zur Hausen first discussed the effect of papillomavirus on tumorogenesis in the cervix in 1983. HPV16 and HPV18 are the most dangerous and carcinogenic. Based on previous studies, SCCs and adenocarcinomas are associated with HPV18 and HPV16, respectively (15,16).

Due to the close relationship between this virus and CC, HPV testing, especially hrHPV testing, has become an essential diagnostic tool in women’s annual examinations and screening programs. The hrHPV genome may initially appear as an episome, which can cause benign and precancerous cervix lesions. The complex process of uncontrolled cell division in cervical carcinogenesis is the result of *HPV* gene integration, along with additional cellular and epigenetic modifications. When viral DNA integrates into the host’s DNA, mutations occur and allow viruses to evade the immune system and cellular defense systems. Overexpressed oncoproteins E6 and E7 with short length (E6:150 and E7:100 residues) can affect the activity of the host cell, promote cell division, and hinder apoptotic processes in cells. Thus, controlling viral transcription factors determines the carcinogenic potential of hrHPV (16).

Important roles of E6 and E7 indicate that these two proteins are essential to the virus’s survival. These early proteins cause cell cycle disorder by inhibiting the function of p53 and pRB, ultimately leading to increased cell numbers. During the hrHPV infection, pRB inactivation causes the transition of the S phase of the cell cycle; in these conditions, the increase in the rate of cell

proliferation will be accompanied by the enhancement of viral transcription (17-19).

Many epigenetic changes have been reported in the presence of HPV. DNA methyltransferases (DNMT) have been demonstrated to interact with E6 and E7 proteins; this interaction reduces their activity and causes hypermethylation of CpG islands, which may ultimately result in the silencing of host tumor suppressors. In contrast to normal cells, some studies reported that cells in cervical carcinoma had lower levels of methylation in the upstream regulatory region, while other studies reported higher levels of methylation in the viral genome, which can be one of the defense mechanisms of the virus (16).

The cell cycle is regulated as a result of the interaction of p21 or p27 with cyclin-cyclin-dependent-kinase complexes in the nucleus of cells. The E7 protein of the virus can bind to p21 and p27 and interfere with the regular functioning of the cell cycle. In healthy cells, when the DNA of the virus is integrated into the host's genome, p53 prevents the reproduction of cells by DNA damage and apoptosis. The virus E6 protein can destroy this essential protein of the cell using proteasomal degradation. A virus-infected cell uses interferon secretion for an antiviral response. E6 binds to IRF3, while E7 binds to IRF1. Matrix metalloproteinases are enzymes whose function is related to cell-matrix breakdown and increased angiogenesis. Reports confirm the association between matrix metalloproteinase 1 overexpression and metastasis in virus-infected patients with cervical carcinoma (17,19,20).

Micro and Long Non-coding Ribonucleic Acids in Cancer

A class of RNAs known as miRNAs controls and alters the expression of genes. RNA pol II and RNase III enzymes perform their biosynthesis with a complex process. The initial precursor of miRNAs is 70 nucleotides in length, which matures into a duplex miRNA with approximately twenty-two units. They can have a highly important function in regulating various pathways, such as cell division and metabolism. MiRNAs can develop cancer by affecting cell proliferation and apoptosis (10,21). These types of miRNAs that are involved in tumorigenesis pathways are called oncogenic miRNAs, which are accompanied by excessive expression. Until now, extensive research has been conducted to identify potential biomarkers. For this purpose, the effect of miRNAs on tumorigenesis has been investigated with different biological methods (22). MiRNAs interrupt the process of cell proliferation and cause carcinogenesis by targeting proteins in regulatory pathways of the cell cycle, such as cyclins and cyclin-dependent kinases (23). Genetic modifications (e.g., DNA methylation, which is performed by DNMTs) are influenced by miRNAs (24,25). Among the miRNAs, we can mention miR-29, which directly affects DNMT-3A and DNMT-3B (26). The control of p53 expression is another vital function of oncogenic miRNAs. P53 has anti-proliferative effects in response to various threatening signals. MiR-504 inhibits the expression of this protein by interacting with special sequences. The 3'UTR of TP53 is also targeted by miRNA-25 and miRNA-30d (27). Angiogenesis has a critical function in the proliferation and metastasis of cancer cells. This process is targeted by miRNAs (28).

Each miRNA with a different mechanism and site of action contributes to the development of different cancers in various tissues. In breast cancer, miRNA-218-5p has a negative effect on the LRIG-1, which can affect the expression of ErbB2 and EGFR proteins (29).

A large class of mRNAs that are transcripts of eukaryotic genomes belong to lncRNAs. They are found in the endoplasmic reticulum, ribosomes, mitochondria, cytoplasm, and other organelles of the subcellular environment. Diverse and extensive biological functions have been described for them, such as chromatin organization, regulation of gene transcription, and translation. Disruption in the regulation and abnormal expression of these types of RNAs plays a role in the development of tumors through multiple biological pathways (30,31). The association of various lncRNAs with various cancer types is presented in Table 1.

The role of lncRNA SPINT1-AS1 on proliferation, migration, and metastasis was evaluated in a study conducted on 30 samples of people with breast cancer and 25 healthy samples. SPINT1-AS1 demonstrated elevated expression in the patient's serum and breast cancer cell lines. This lncRNA exerts its effect through the regulation of miR-let-7a/b/i-5p (32). The effect of SFTA1P on the progression of carcinoma in the cervix has been confirmed as well. This type of RNA causes the degradation of TPM4 mRNA by interacting with PTBP1 (33). Among the other lncRNAs, LINC00460 is mentioned as an oncogene that acts through T cells and the PD-1 checkpoint in the development of pancreatic cancer (34). In gastric cancer, the increase in the expression of SERPINE1, which is induced by lncRNA NKX2-1-AS1, causes the activation of the VEGFR-2 signaling pathway, and ultimately, the progress of tumorigenesis (35). LncRNA TMPO-AS1 exerts its influence on the progression of esophageal squamous cell cancer by affecting TMPO transcriptional regulation (36). The spread of liver cancer through the PDK1/AKT/Caspase 3 pathway is associated with PDPK2P (37).

Table 1. Reported Cases About the Relationship Between Different Types of Cancer and Long Non-Coding Ribonucleic Acids

Authors, Year (Ref.)	Year	Long Non-coding RNAs	Types of Cancer
Zhou et al (32)	2021	SPINT1-AS1	Breast cancer
Luo et al (33)	2022	SFTA1P	Cervical cancer
Yao et al (34)	2022	LINC00460	Pancreatic cancer
Teng et al (35)	2021	NKX2-1-AS1	Gastric cancer
Luo et al (36)	2022	TMPO-AS1	Esophageal squamous cell cancer
Pan et al (37)	2019	PDPK2P	Liver cancer

Deregulated Micro RNAs and Long Non-coding Ribonucleic Acids in Cervical Cancer

Any irregularity in expression can be used as a diagnostic biomarker. The success of treating and managing cancer largely depends on the stage of diagnosis. Today, due to the importance of early diagnosis of any change in the tissue of the cervix, extensive studies are conducted on diagnostic biomarkers. Cancer biomarkers are highly diverse and are based on changes in epigenetics, gene expression profiles, the complex proteome system, metabolites, metabolic pathways, and immune system cells. Blood or vaginal mucus samples can be utilized to identify changes in gene expression profiles in the detection of this cancer. Comparing normal and cancer tissues of the cervix, several changes in the abundance of miRNAs and lncRNAs have been reported in various precancerous stages of the cervix to advanced stages, which can be used as diagnostic biomarkers (38,39).

MiRNAs, which have a key function in post-transcriptional gene regulation, are often associated with the cancer development process. These types of miRNAs are potentially effective in diagnostics and treatment. In different studies to investigate function, mechanism, and changes in the expression patterns of various CC-related miRNAs, two cancerous cervical tissues have been compared with the normal cervix. These deregulated miRNAs are generated by numerous factors occurring in miRNA regions, including genetic deletions and mutations, genetic amplifications, epigenetic changes (e.g., modifications of DNA methylation), and changes in the function of transcription factors involved in miRNA biogenesis. Changes in the levels of miRNAs have been highlighted in numerous studies on CC (9,10,12).

MiRNA expression patterns in CC and the precursor lesions were detected by Kawai et al using cervical mucus. In this research, four up-regulated miRNAs (i.e., miRNA-126-3p, miRNA-20b-5p, miRNA-451a, and miRNA-144-3p) were obtained as biological detectors for the diagnosis of malignant changes in the cervix (40). In the study by Banno et al, it was shown that the expression levels of miRNA-21, miRNA-126, and miRNA-143 are changed in patients with CC, thus probably playing a role in this disease. Therefore, therapeutic strategies based on targeting these miRNAs may be useful (41). Exosomal miRNAs have been documented in association with CC. Lv et al found that circulating exosomal miRNA is a biological biomarker for CC detection. Their report suggests that circulating exosomal miRNA-125a-5p can be used to identify CC (42).

The potential effects of miRNA-10a-5p on proliferation, invasion, migration, and apoptosis in CC cells were evaluated by Gu et al. It was discovered that miRNA-10a-5p directly targets UBE2I, and the upregulation of this miRNA promotes tumor progression. The findings from this study provided evidence that miRNA-10a-5p could be a promising target for CC treatment (43).

Farzanehpour et al reported the high expression of miRNA-9, miRNA-192, and miRNA-205 in cancer tissues and serum samples compared to normal conditions (44). Furthermore, overexpressed miRNA-9, miRNA-10a, miRNA-20a, and miRNA-196a were obtained in sera from cervical intraepithelial neoplasia patients compared to healthy controls (45).

Liu et al studied 582 patients with tumorigenic changes in the cervix (cases) and another 145 controls. Differential expression analysis revealed that six miRNAs, including miRNA-20a, miRNA-92a, miRNA-141, miRNA-183, miRNA-210, and miRNA-944, were considerably overexpressed in CC tissues and premalignant lesions compared with the standard cervix samples; it was concluded that these detected miRNAs have oncogenic potential (46).

The results of the study performed by Aguilar-Martínez et al confirmed the overexpression of miRNA-21 in cervical lesions. Based on this research, not only the growth but also the migration of malignant cells of the cervix, which is performed via the RECK signaling pathway, is influenced by miRNA-21 (47).

The role of miRNA-519d, miRNA-17-5p, and miRNA-501 in CC metastases has been shown in one study. Their function is related to different targets, such as SMAD family member 7, transforming growth factor, and forkhead box protein G1, respectively (48).

Furthermore, the expression profile of miRNAs changes with persistent infection. The most important type of infection in this field is related to HPV. Various studies have reported that dysregulation of miRNAs in normal cervical cells is caused by the proteins of HPV. In the Uyghur population in China, a study was performed on the expression profile of miRNA in HPV-infected CC tissue and uninfected cervical tissue. This research identified that miR-15a-5p, miRNA-17-5p, miRNA-20a-5p, miRNA-21-5p, miRNA-96, miRNA-106b-5p, and miRNA-3653 are related to the development of cancer in HPV-infected patients (49). HPV E7 had an effect on the expression of miRNA-15a, miRNA-16-1, and miRNA-203, while HPV E6 could affect the expression of miRNA-23b, miRNA-34a, miRNA-218, and miRNA-92 (50). Table 2 presents the association between various HPV strains and their targets in metastases of CC.

Based on research, the incidence and development of tumorigenic changes in the cervix are influenced by different lncRNAs. These types of oligonucleotides are involved in many cellular processes, such as differentiation, proliferation, metastasis, and apoptosis in CC. It has been demonstrated that lncRNA biomarkers can be used to diagnose, predict, and guide the treatment process of CC (58). The high expression of LncRNA CCAT2 with the 1752 nucleotide sequence and chromosomal location 8q24 and SPRY4-IT1 (two oncogenic lncRNAs) has been reported in CC tissues (59,60). Based on the evidence, silencing SPRY4-IT1 expression inhibits migration and invasion in CC cell lines (61). Chen et al found an increase in CCHE1 with a sequence of 2500 nucleotides

Table 2. Reported Cases About the Relationship Between Different Types of HPV and miRNAs in Cervical Cancer

Authors, Year (Ref.)	HPV Type	Oncoprotein	MiRNAs
Norouzi et al, 2021 (51)	HPV16	-	miRNA-16, miRNA-21, miRNA-34a, and miRNA-143
Zhang et al, 2015 (52)	HPV16	E7	miRNA-27b
Cheng et al, 2017 (53)	HPV18	E6	miRNA-20b
Babion et al, 2020 (54)	HPV16 and HPV18	-	miRNA-221-3p, and miRNA-138-5p
Jiang et al, 2016 (55)	HPV16	E6	miRNA-218
Morgan et al, 2020 (56)	HPV16 and HPV18	E6 and E7	MiRNA-18a
Zhang et al, 2020 (57)	HPV18	E6 and E7	miRNA-377

Note. HPV: Human papillomaviruses; MiRNA: Micro ribonucleic acids.

on chromosome 10 in advanced large CC tumors and called it a potential prognostic biomarker for CC (62).

In a study investigating the expression of CYTOR in CC compared with adjacent healthy tissues using quantitative real-time polymerase chain reaction, the expression of CYTOR was found to be considerably overexpressed in cancerous samples (63).

Some of the onco-lncRNAs performed their regulatory role by binding to key proteins or targeting key pathways. For example, EBIC is an oncogene lncRNA that binds to the enhancer of zeste homolog 2 and inhibits E-cadherin expression in CC (64). According to the results of Ma et al, LINC00675 is involved in the proliferation, migration, and invasion of CC cells through its effect on the Wnt/β-catenin signaling pathway (65). The high expression of LINC00473 enhanced cell proliferation and prevented apoptosis in CC cells in vitro. LINC00473 binds to ILF2 and thus prevents its degradation. ILF2 was known as an oncogenic protein in cancer (66). ARAP1-AS1 is involved in various types of cancer. The expression of ARAP1-AS1 was high in CC tissues and plays a role in the process of tumorigenesis. ARAP1-AS1, miR-149-3p, and POU2F2 are connected in this process. ARAP1-AS1 changes POU2F2 expression by reducing miR-149-3p expression (67). The overexpression of lncRNAGHET1 in CC cell lines was reported in previous research. The two AKT/mTOR and Wnt/β-catenin pathways were regulated by this lncRNA, and silencing of GHET1 could inhibit cell proliferation and migration (68).

The interaction of lncRNAs and miRNAs has been reported in many studies in the process of carcinogenesis. Onco-lncRNA PVT1 is a highly conserved lncRNA that promotes metastasis in CC cells by downregulating miRNA-424 expression. Further, PVT1 completely suppresses the expression of miRNA-200b and miRNA-195 (69). In addition, LncRNA CASC2 and NEAT1 have an effect on miRNA-21 and miRNA-193b-3p, respectively (70,71). MALAT1, with 8000 nucleotides on chromosome 11q13.1, leading to a variety of epigenetic modifications, is associated with CC. MALAT1 promotes CC metastasis and progression through miRNA-429 (72,73). Another oncogenic lncRNA that is involved in the process of migration and invasion of CC cells and cancer progression is LINC00080 (TUG1). This lncRNA promotes its function via epithelial-mesenchymal transition (74).

In patients infected by hrHPV, viral oncoproteins, such as E6 and E7, can change the lncRNA expression. These functions are one of the main reasons for initiating carcinogenesis in the cervix. Therefore, some ncRNAs greatly contribute to tumorigenesis via viral oncoproteins. Based on research, differential lncRNAs in host cells, including GAS5, H19, and FAM83H-AS1, were changed by E6 expression (75).

According to the study conducted by Zhang et al, lncRNAs affected by E7 include lnc-FANCI-2, HOTAIR, lncPVT1, MALAT1, SNHG12, CCDST, LINC01101, and LINC00277. Based on their reports, MALAT1, CCEPR, and TMPOP2 were regulated by E6 and E7 (76). In the study performed by Liu et al, the high expression of lncRNA HOTAIR in vaginal discharge was found in cervical carcinoma (77).

ENST00000503812, ENST00000420168, ENST00000564977, UCA1, SNHG8, LINC01089, PTOV1-AS1, and HOST2 are up-regulated lncRNAs in patients infected by HPV (78).

LncRNA SNHG12 is deregulated in several cancers. This lncRNA shows significant upregulation in cervical SCC. The E6 and E7 of HPV16 may regulate the expression of SNHG12. Based on these discoveries, SNHG12 is an oncogenic lncRNA and tumorigenesis of CSCC. Hence, SNHG12 is a potential molecular target for the treatment of this type of cancer (79).

Based on the research of Molika et al, several lncRNAs were specifically and differentially expressed in patients with CC at different stages. Gene ontology analysis of this research demonstrated that upregulated differentially expressed extracellular vesicle lncRNAs participating in stages I and II are related to cell proliferation, inflammation, and ways related to cancer progression. Elevated expressions of LINC00941, LINC01910, LINC02454, and DSG2-AS1 were associated with poor overall survival in individuals with CC. DSG2-AS1 was linked to the HPV infection pathway through *COL6A2*, *DLG1*, and *AKT3* genes (80).

Conclusion

Early detection and treatment strategies for CC are crucial for improving patient outcomes while reducing mortality rates. Effective early detection and treatment enhance survival rates while decreasing healthcare costs and the

emotional burden on patients and families. Dysregulated gene expression can help identify therapeutic targets, treatment outcomes, and CC diagnosis. Growing data indicate that HPV and aberrant miRNA and lncRNA expression are useful biomarkers and have critical functions in the spread and metastasis of cervical carcinoma. The study's findings suggest that HPV infection alters host miRNA and lncRNA expression, developing tumorigenesis, progression, and metastasis of CC. Therefore, further analysis and identification of the exact mechanism of function and the correlation between HPV oncoproteins and expression changes can be useful for studying molecular biomarkers in the context of screening programs.

Authors' Contribution

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Competing Interests

The authors declare that they have no conflict of interests.

Ethical Approval

Not applicable.

Funding

The author received no financial support for the research, authorship, and publication of this article.

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