**MicroRNAs as Master Regulators in Cervical Cancer Offering New Avenues for Diagnosis Prognosis and Targeted Therapy**

**(Article Type : REVIEW ARTICLE )**

**ABSTRACT**

As one of the most prevalent cancers affecting women worldwide, cervical cancer is especially prevalent in low- and middle-income nations. The chronic infection with high-risk strains of the human papillomavirus (HPV), particularly types 16 and 18, is the main contributing cause. The urgent need for more precise biomarkers is highlighted by the sensitivity and specificity limitations of current screening methods, such as the Pap smear and HPV DNA testing, which have helped with early detection and decreased mortality. Small non-coding RNA molecules called microRNAs (miRNAs), which post-transcriptionally control gene expression, have become important players in the study of cancer in recent years. They are known to alter vital cellular processes such invasion, immune response, metastasis, apoptosis, and proliferation. Cervical cancer has been linked to aberrant expression of particular miRNAs, which are becoming more and more linked to the development, course, and clinical results of the illness. While some miRNAs work as tumor suppressors, others are oncogenes (oncomiRs), which encourage the formation of tumors. Because of their dual function, they can be used as therapeutic targets in addition to being biomarkers for diagnosis and prognosis. Furthermore, miRNAs' potential as non-invasive indicators is increased by their stability in bodily fluids including blood and cervical mucus. This review provides an overview of miRNA biogenesis and regulatory mechanisms, outlines the most significantly upregulated and downregulated miRNAs in cervical cancer, and discusses recent advances in miRNA-based therapeutic strategies. Understanding the molecular interplay between HPV infection and miRNA dysregulation may pave the way for the development of precision medicine tools, improving early detection, risk assessment, and personalized treatment in cervical cancer care.

***Keywords:*** Cervical Cancer, MicroRNAs, Human Papillomavirus (HPV), Gene Regulation, Biomarkers, Diagnosis, Prognosis, Targeted Therapy, miRNA Biogenesis, Cancer Therapeutics

1. **INTRODUCTION**

Cancer is marked by unchecked cell division and expansion, which leads to the formation of lesions that have the potential to invade nearby tissues and spread to other areas of the body. Leukemia, lymphomas, sarcomas, and cancers are its four primary classifications [1]. Cervical cancer is the fourth most prevalent cancer in women globally, particularly affecting low- and middle-income countries. It contributes significantly to cancer-related morbidity and mortality among females [3-4].

* 1. **ROLE OF HPV & RISK FACTORS IN DIAGNOSIS OF CARCINOGENESIS**

The primary cause of the associated risk factors is human papillomavirus (HPV) infection. Covering more than 99.7% of all cases.[5]. Further considerations reported to elevate the risk of cervical cancer include poor, immunosuppression, smoking sexual health, and failure to attend regular screenings [6]. Every time cervix cancer arises, the cervical cells go through a process called dysplasia, which causes aberrant cells to form inside the cervical tissue. These aberrant cells can become malignant over time, invading deeper cervical tissues [5]. Cervical cancer is rare in children [6]. Although HPV alone doesn’t cause cancer, it significantly contributes to disease progression [7]. HPV (Human Papillomavirus) strains can be classified as either low-risk or high-risk. High-risk strains can result in cancer, although low-risk strains might cause anogenital warts or stay asymptomatic. High-risk HPV infection is the cause of more than 99 percent of cervical dysplasia and cervical carcinoma precancerous lesions.[9]. Forty of the approximately 200 HPV strains that are known to exist impact the anogenital area. High-risk genotypes have been assigned to 1518 HPV strains in total. Most cervical neoplasia and cancers are caused by high-risk HPV genotypes, with types 16 and 18 accounting for over 70% of all cervical cancer occurrences. About 20% of cervical adenocarcinomas are type 18, whereas 50% of squamous cell carcinomas and 55% to 60% of all cervical malignancies are type 16.Types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 are additional carcinogenic HPV strains that together account for 25% of cervical carcinomas.

HPV infections can lead to cancer in the anus, vulva, vagina, penis, and oropharynx [10]. HPV infection is linked to several cervical cancer risk factors. It could take up to 20 years for aggressive cancer to grow from a precursor lesion caused by sexually transmitted HPV. Sexually transmitted diseases are a risk factor for cervical cancer. Ameta-analysis found that the highest prevalence of HPV occurs between the ages of 25 and 35, which may be related to changes in sexual behavior, Human Immunodeficiency Virus (HIV), the cause of Acquired Immunodeficiency Syndrome (AIDS), increases susceptibility to high-risk HPV infection in women [11]. High parity, long-term cigarette smoking, and oral contraceptive use are major behavioral risk factors in the persistence of disease. Hereditary host variables may also influence HPV persistence and disease progression. Cervical cancer may run in families, according to earlier studies. According to research on the family clustering of cervical cancer, women who have an afflicted first-degree cousin are up to two times more likely to develop invasive cervical cancer or cervical intraepithelial neoplasia grade 2/3 [12]. Early detection and treatment may result from efficient screening. A pap smear test can detect early cervical epithelial alteration and is the primary screening tool for precancerous cervical intraepithelial neoplasia and the early stages of invasive cervical cancer.[13].

* 1. **NEED FOR NOVEL BIOMARKERS AND RELEVANCE OF miRNAs**

Short, non-coding RNA molecules known as microRNAs (miRNAs) control gene expression and other biological functions.[14] [15]. miRNA synthesis involves transcription from DNA sequences, followed by processing into precursor and mature forms. Typically, miRNAs interact with the 3’ untranslated region (UTR) of target mRNAs, triggering, degrading, or translational repression, however, interactions with other areas have been described. Extracellular miRNAs can be released and transferred to target cells, allowing for cell-cell communication [15]. The therapeutic potential of miRNAs is being intensively investigated, with some candidates entering the preclinical and clinical trials [14]. Recently, miRNAs have been proposed as promising biomarkers with high sensitivity and specificity for the non-invasive detection of cervical cancer. Non-coding RNAs with 19–24 nucleotides are called miRNAs. It was found that miRNAs are frequently uncontrolled in cancer.[16].

***Figure 1 :* Absolute Number and Incidence of Cervical Cancer Cases Among Females Worldwide, 2022.**

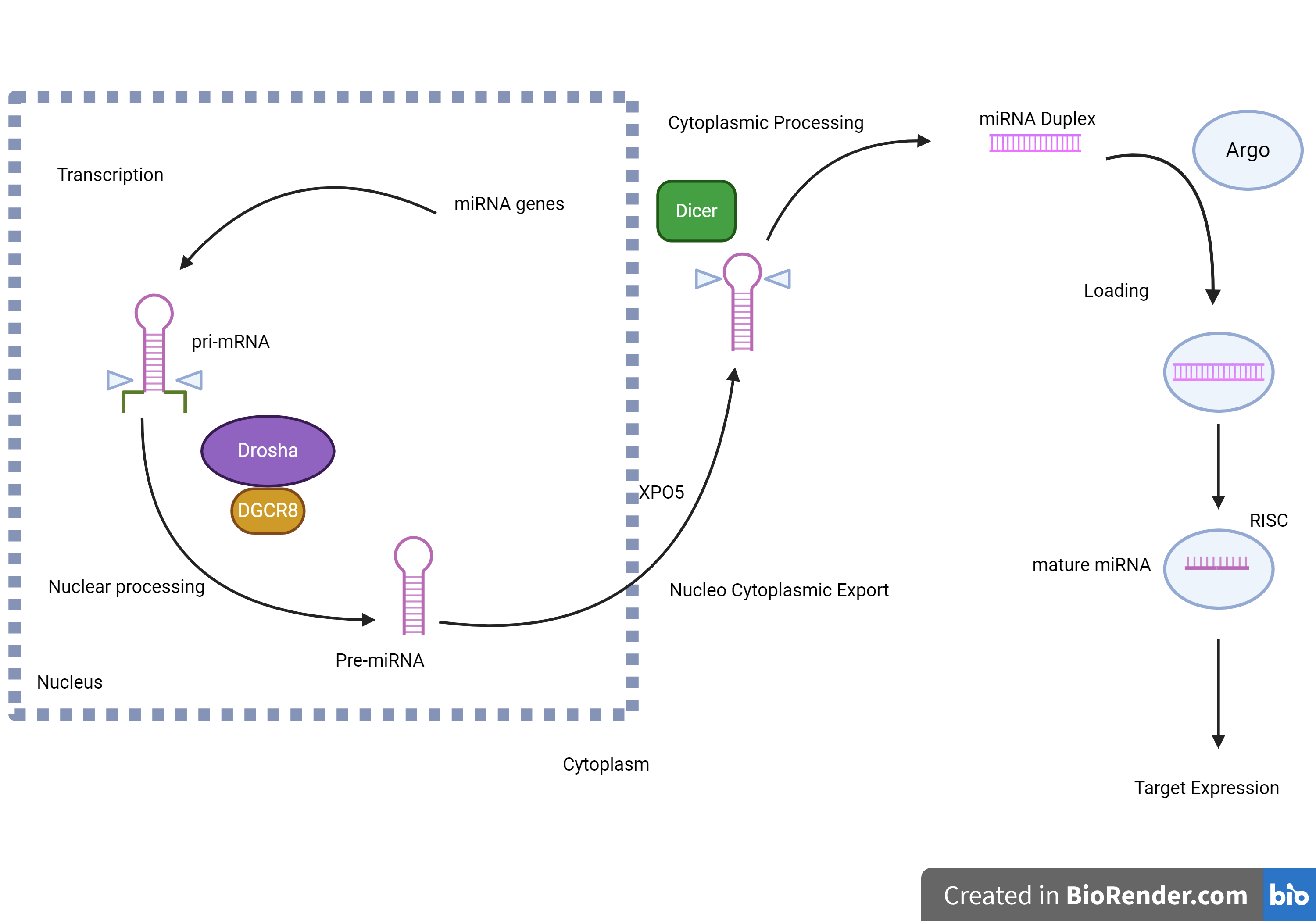
**2. *MiRNAs* :**

miRNAs were identified in 1993. The regulation of post-transcriptional levels of gene expression depends on this type of short non-coding RNA, which has a length of 19–24 nucleotides. miRNAs function by either degrading their RNA targets or preventing mRNA translation. MiRNAs are involved in important biological processes, including those related to cancer, and control post-transcriptional gene expression. The pathophysiology of disease, including cancer, has been demonstrated to be significantly influenced by miRNAs [17]. About 30% of human genes are controlled by miRNAs, despite the fact that only 3% of genes code for proteins. MiRNA studies began to concentrate on the functional roles of miRNAs after it was found that the first miRNAs to be identified, let-7 and lin-4, were involved in cell cycle regulation in C elegans. Because a miRNA can have several targets, it can control a variety of important human pathways that control metabolism, growth, development, and immunity, among other biological processes [18].

**2.1. *miRNAs* Biogenesis *:***

Human miRNA biogenesis is a multi-step process involving a number of important enzymes and regulatory elements [20-22]. RNA polymerase II as longer primary transcripts with a stem-loop structure, known as prior-miRNAs.[22]. The prior-miRNA is then cleaved by the Microprocessor complex, which is made up of the RNase III enzyme Drosha and the double-stranded RNA-binding protein DGCR8, to produce a precursor miRNA. The pre-miRNA is exported from the nucleus to the cytoplasm by the Exportin-5 protein. The pre-miRNA in the cytoplasm is further broken down by another RNase III enzyme called Dicer, which cleaves it and produces a duplex of miRNA. An Argonaut (AGO) protein, a component of the RNA-Induced Silencing Complex (RISC), is then loaded with the miRNA duplex. The miRNA duplex is then loaded onto an Argonaut (AGO) protein, which is a part of the RNA-induced Silencing Complex. Within the RISC, the passenger strand of the miRNA duplex is often broken down, while the guide strand is maintained intact. When the mature miRNA directs the RISC toward the target mRNAs, translational suppression of the mRNAs' destruction occurs. [21]. It's interesting to note that for a subclass of miRNAs called mirtrons, the spliceosome eliminates the hairpin precursor from the host gene intron without the need for Drosha.

Splicing factors such as SRSF1 and SRSF2 can regulate the production of mirton-derived miRNAs in cancer cells by controlling their processing and levels [20]. The initiation and spread of dysregulation of the miRNA biogenesis pathway, which involves alterations in the expression of the Drosha, Dicer, DGCR8, and Aeronaut proteins, have been connected to a number of human malignancies [22]. In conclusion, disruptions in the miRNA biogenesis pathway—a series of processing stages controlled by significant enzymes and regulatory factors—can result in human diseases, including cancer [20–23].

***Figure 2 :* Overview of the *miRNA* biogenesis pathway.**

1. **Biomarker’s :**

The biomarkers consortium and a working committee of the US National Institutes of Health (NIH) define a biomarker as a characteristic that can be objectively assessed as an indication of typical infection processes or a pharmacological response to a therapeutic intervention.[25]. Better ways to forecast a person's risk of developing cancer and detecting tumors early when they can be treated more successfully are the main objectives of biomarker development, in addition to improved treatments.[24]. Blood tissues and other bodily fluids typically contain biomarkers that show whether a process or disease is normal a pathological. A biomarker can be identified via genetics, Proteomics, or cellular or molecular components that are present in higher-than-normal concentrations in a cancer patient's bodily fluids (blood, urine) [26]. None of the biomarkers that are currently on the market meet the ideal sensitivity and specificity of 100% [27].

**3.1. *Biomarker’s significance in treating cervical cancer* :**

Despite its intra-observational subjectivity, microscopic examination of biopsied materials has long been the cornerstone of screening and diagnostic procedures. As a result, even while significant technological advancements have been made to detect cancer in its early stages, many malignancies are discovered at the microscopic level too late for therapeutic intervention. [28]. Cervical cancer typically does not exhibit acute symptoms as burning, itching, or vaginal discharge, in contrast to many genitourinary illnesses.[29]. Although they are not cancerous, a few of cells in the cervical cavity may exhibit early change. The epithelium layer of cells experiences dysplasia or squamous intraepithelial lesion (SIL) as a result of these precancerous cells.

**3.2 *miRNA as biomarkers in cervical cancer* :**

Small non-coding RNAs known as miRNAs control the expression of genes and have become promising biomarkers for several illnesses, most notably cancer [30]. Accessibility, high specificity, and sensitivity are traits of excellent biomarkers that these compounds display [31]. As detailed in Section 2, miRNAs influence key pathways in tumorigenesis; here, we highlight their value as diagnostic and prognostic biomarkers in cervical cancer. [32] miRNAs have emerged as promising markers for cervical cancer staging, diagnosis, and prognosis. Studies have shown that a number of miRNAs may be important for cervical cancer diagnosis and prognosis. Urine samples that included a combination of miR-145-5p, miR-218-5p, and miR-34a-5p, for instance, shown great sensitivity and specificity in analysis when separating precancer and cancer patients from healthy controls, as well as good association with serum and tumor tissue samples. Interestingly, miRNA profiling in urine samples has shown potential as a non-invasive method for early detection and prognosis of cervical cancer.[33]. miRNAs, or small non-coding RNAs, regulate gene expression and have emerged as prospective biomarkers for a number of diseases, most notably cancer [30]. These compounds have excellent biomarker qualities, such as high accessibility, sensitivity, and specificity. [31]. As detailed in Section 2, miRNAs influence key pathways in tumorigenesis; here, we highlight their value as diagnostic and prognostic biomarkers in cervical cancer [32]. Non-invasive sample techniques such as urine-based diagnostics improve early detection and patient compliance [33–36]. In conclusion, miRNAs have demonstrated significant potential as biomarkers for the early detection, diagnosis, and prognosis of cervical cancer and play a significant role in its development. Combining miRNA analysis with other molecular markers and developing non-invasive sampling techniques, such as urine-based diagnostics, may enhance future cervical cancer screening and therapy methods.[34-36]

1. **The interaction of HPV and miRNA affects the development of cells and cancer :**

miRNAs have a key role in the development and spread of cervical cancer, especially in relation to Human Papillomavirus (HPV) infection. HPV is the primary cause of cervical cancer, and its oncogenic proteins E5, E6, and E7 are crucial to carcinogenesis [37]. Human papillomavirus (HPV) infection is a major risk factor for the development of cervical cancer, particularly high-risk HPV strains 16 and 18, which are responsible for almost 70% of instances of cervical cancer [38].

Many studies of cervical precancerous tissues have consistently shown that a number of miRNAs, including miRNA 34a, miRNA-9, miRNA-21, miRNA-145, and miRNA-375, are dysregulated. The early transformation processes triggered by HPV's E6 and E7 oncoproteins may involve these miRNAs. Due to the significant differences in their expression profiles between HPV-infected cervical cancer tissues and normal tissues, miRNAs may be employed as biomarkers for early diagnosis and prognosis [39].

Although the precise role that miRNAs play in the development of HPV-related cervical cancer is yet unknown, their potential as specific biomarkers for diagnosis, prognosis, and even treatment is encouraging. Important information regarding the potential use of miRNAs to improve cervical cancer treatment strategies may be obtained from further research in the field [40]. HPV disrupts normal miRNA processing by changing DROSHA levels, which weakens gene regulation and promotes the development of cervical cancer [41].

1. **Cervical cancer and miRNA types :**

Cervical cancer exhibits unique expression patterns for the various microRNA (miRNA) types seen in serum/plasma, urine, and cervical mucus. High diagnostic accuracy and promising non-invasive biomarkers for early detection, prognosis, and tracking of cervical cancer progression and response to treatment are provided by these miRNAs, which include miR-21-5p, miR-199a-5p, and miR-145.

* 1. ***Serum/plasma MicroRNAs (miRNAs)* :** Serum and plasma microRNAs (miRNAs) have become promising markers for the diagnosis and prognosis of cervical cancer. By comparing cervical cancer patients to healthy controls, multiple investigations have found dysregulated miRNAs. High cervical cancer detection accuracy was demonstrated by a panel of four plasma miRNAs (miR-146a-5p, miR-151a-3p, miR-21-5p and,miR-2110) (Ma et al., 2019). According to (Jiang et al., 2017), Reduced expression of miR-101 was a substantial adverse risk factor for patient prognosis, and it was discovered that miR-101 was down-regulated in cervical cancer tissues relative to normal cervical tissues. Cervical cancer patients had lower plasma miR-145 levels than those with cervical intraepithelial neoplasia (CIN) and healthy controls, and low levels were linked to advanced FIGO stage, HPV, poor cancer differentiation, and lymph node metastases (Wei et al., 2017).
  2. ***Urinary miRNAs :*** HPV was detected in 80% of urine samples from cancer patients and 60% of urine samples from pre-cancer patients. Urinary miRNAs are useful for diagnosis; PCR-based urine analysis revealed that 80% of cancer samples and 60% of pre-cancer samples were HPV-positive. These findings suggest that urine is not only a useful, noninvasive diagnostic tool but also may be able to detect miRNA biomarkers, which are crucial for understanding the molecular mechanisms behind cervical cancer development and for developing targeted diagnostic and therapeutic strategies. Urine miRNAs, particularly miR-21-5p and miR-199a-5p, have the highest diagnostic efficacy due to their high sensitivity, specificity, and AUC values. According to Aftab et al. (2021), these miRNAs have a lot of potential for noninvasive cervical cancer screening. Due to their concentration in the centrifuged pellet and stability against multiple nucleases, urinary miRNAs are ideal for biomarker research. According to Mall et al. (2013), the study demonstrates that qRT-PCR is a reliable method for accurately quantifying urine miRNAs for clinical diagnostic applications.
  3. ***Mucus miRNAs:*** According to Wittenborn et al. (2020), cervical mucus miRNAs like miR-20b-5p and miR-144-3p show elevated levels in cervical neoplasia. A cervical mucus miRNA panel may be able to distinguish between patients with cervical intraepithelial neoplasia (CIN) 3 and healthy people, according to Wittenborn et al. (2020). Cervical mucus contains a number of microRNAs (miRNAs), including miR-20b-5p, miR-451a, miR-126-3p, and miR-144-3p. Cervical cancer and its precursor disorders have significantly higher levels of these miRNAs. According to Kawaki et al. (2018), these miRNAs have a high degree of accuracy in detecting cervical cancer and high-grade cervical intraepithelial neoplasia (CIN). Additionally, the five miRNAs(miR-126-3p, miR-451a, miR-144-3p,, miR-55-5pand miR-20b-5p) present in cervical mucus, HPV genotype, and age can be used to generate a nomogram that reliably predicts the risk of cervical cancer and its precursor lesions. For cancer and CIN 3+, the nomogram's accuracy is 0.983 and 0.966, respectively.

1. ***MiRNAs* that are upregulated and downregulated in cervical cancer**

**Cancer :**

Numerous microRNAs' (miRNAs') expression profiles are markedly changed in cervical cancer, which aids in the growth and spread of the tumor. MiR-21, miR-155, and miR-196a are examples of frequently elevated miRNAs that are linked to increased cell invasion, proliferation, and apoptosis resistance. On the other hand, downregulation of miR-143, miR-145, and miR-218 often results in the loss of tumor-suppressive properties. Gaining knowledge of these miRNA dysregulations can help with targeted therapy, diagnosis, prognosis, and cervical carcinogenesis.

**6.1. *OncomiRNAs :***

One way to characterize oncogenes is as miRNAs that are significantly overexpressed in cancers. They all appear to act as oncogenes, albeit some have been described in detail. Known as oncomirs, these oncogene miRNAs usually promote tumor growth by negatively inhibiting genes that control cell differentiation or death as well as tumor suppressor genes.[42]. Depending on the stage of cervical cancer development, oncomiR expression patterns can change. Certain dysregulated miRNAs have been linked to particular phases of cervical cancer development, indicating that they may be used as biomarkers for cancer monitoring and categorization. Additionally, via controlling several cellular pathways, oncomiRs contribute to medication and radiation resistance in cervical cancer [43].

Numerous cancer forms have been found to have miRNA-21 as an oncogene. Research has demonstrated that in these malignancies, miRNA-21 inhibits apoptosis while promoting cell invasion, proliferation, and survival [44]. The suppression of tumor suppressor genes, particularly phosphatase and tensin homolog (PTEN) and programmed cell death 4, is the main way that miR-21 induces cancer. It has been shown that when miRNA-21 is blocked or PTEN and PDCD4 are overexpressed, cancer cells undergo apoptosis and tumor growth suppression.[40].

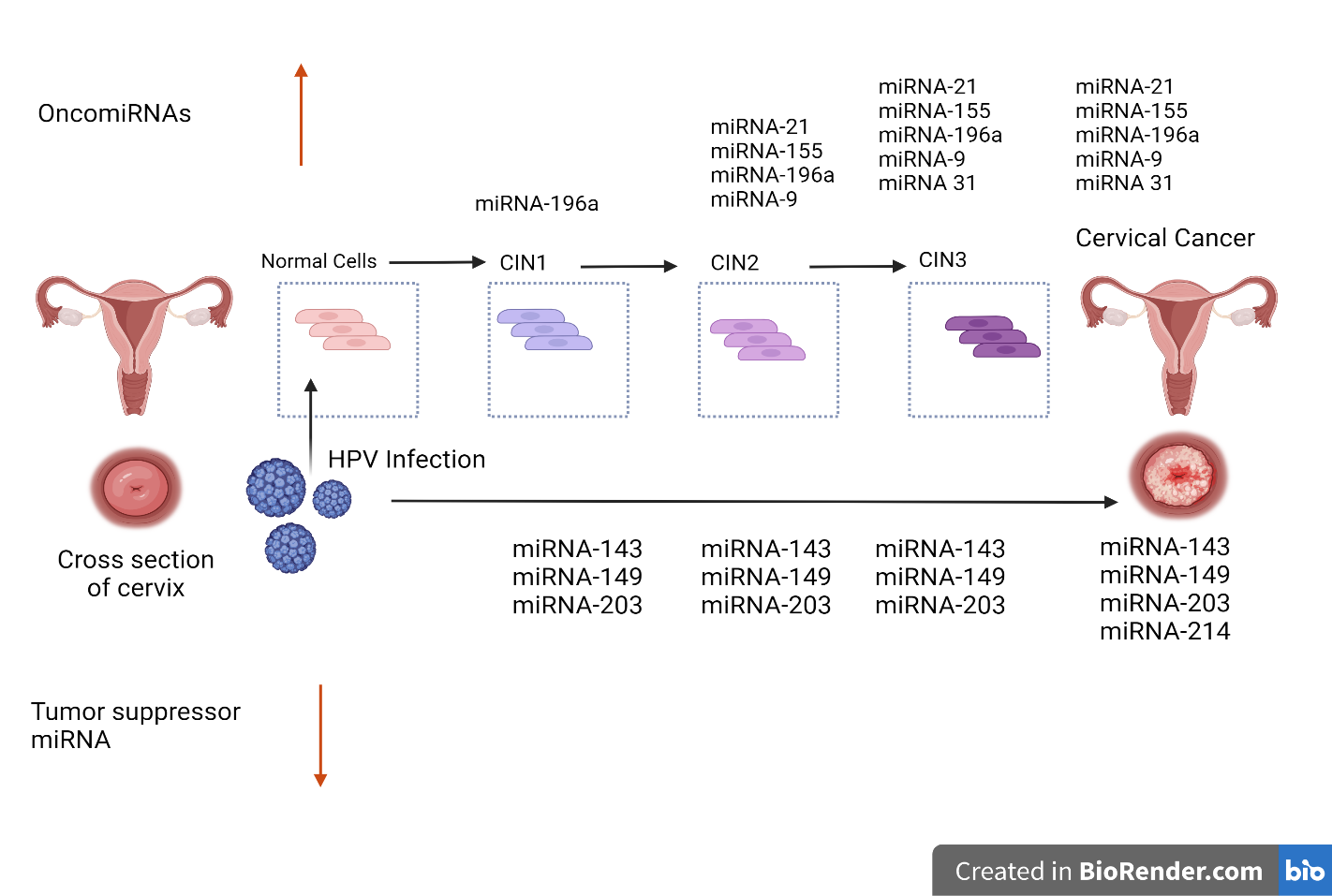
Cervical cancer development is strongly impacted by miRNA-155. Studies have shown that the levels of miRNA-155 were higher in cervical cancer tissues than in non-cancerous tissues that were close by. Overexpression of miRNA-155 promotes cervical cancer cell invasion, migration, and proliferation, whereas downregulation inhibits these processes. LKB1 and other tumor suppressor genes are selectively targeted by miRNA-155, which also suppresses their expression.[47] [48]. At different phases of the development of cervical cancer, there is a marked increase in the expression levels of miRNA-155. In particular, its expression rises in stages two and three of cervical intraepithelial neoplasia (CIN) and even more in invasive cancer [49]. miRNA-196a has an important role in the regulation of many cancers. Studies have shown that miRNA-96a is upregulated in oral squamous cell carcinoma (OSCC), lung cancer, cervical cancer, and hepatocellular carcinoma (HCC). Overexpression of miRNA-196a in several cancer types promotes cell invasion, migration, and proliferation while suppressing apoptosis. MiRNA-196a's carcinogenic effects are mediated by its direct targeting of tumor suppressors such FOXO1 and p27.[50] [51]. There are notable increases in miRNAs 196a expression levels at various stages of cervical cancer progression. Its expression specifically increases in cervical intraepithelial neoplasia (CIN) stages 1, 2, and 3, as well as in invasive cancer. [52]

The development and metastasis of cervical carcinoma are significantly influenced by miRNA-9. It is excessively expressed in Cervical Cancer tissues and cells and may be p53-independently triggered by the human papillomavirus (HPV) [53]. MiRNA-9 stimulates the invasion and migration of cervical cancer cells selectively targeting and blocking FOXO1 [54]. Apoptosis is inhibited and cell division is stimulated by regulating FOXO3 and its downstream proteins Bax, Bcl-2, and p-Akt [55]. At various stages of cervical cancer progression, there is a noticeable rise in miRNA-9 expression levels. Its expression specifically increases in cervical intraepithelial neoplasia (CIN) stages two and three, and it increases even further in invasive carcinoma.[49].

MiRNA-31 is an oncogenic factor in head and neck squamous cell carcinoma (HNSCC) and cervical cancer. MiRNA-31 is increased in Cervical cancer and targets BAP1 to induce the epithelial-mesenchymal transition, accelerating tumor development and metastasis [56]. Likewise, miRNA-31 increases oncogenicity and stemness in HNSCC by targeting ARIDIA. Several miRNAs, including miRNA-31, have been identified as dysregulated in Cervical Cancer and may serve as biomarkers for prognosis, early identification, and therapy response tracking [58]. At various stages of cervical cancer progression, there is a noticeable rise in miRNA-31 expression levels. Its expression is especially elevated in cervical intraepithelial neoplasia (CIN) 3 and invasive carcinoma [59].

**6.2. *miRNAs* that inhibit Tumors :**

Oncogenesis causes malignant cells to downregulate certain miRNAs. These miRNAs are found in tumor suppressor genes. Tumor suppressor miRNAs usually prevent tumor growth by negatively influencing oncogenes and genes that control cell differentiation or death [60]. These miRNAs are commonly downregulated in many cancer types, which promotes the expression of their target genes and accelerates tumor growth. For instance, miRNA-152 is a tumor suppressor in several cancers and targets genes implicated in cell invasion, migration, and proliferation [61]. miRNA-143 plays a significant part in the development of cervical cancer. Compared to normal controls, it is markedly downregulated in cervical cancer cell lines and tissues. By encouraging apoptosis and preventing cell invasion, migration, and proliferation, Mi143 suppresses malignancies [62]. By indirectly targeting B-cell lymphoma-2 (Bcl-2), over-expression of miRNA-143 has been shown to significantly reduce the proliferation and increase apoptosis of cervical cancer cells [63]. At different phases of cervical cancer progression, there is a discernible increase in miRNA-31 expression levels. Invasive carcinoma and cervical intraepithelial neoplasia (CIN) have particularly high levels of its expression 123 [64].

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***Figure 3 :* Dysregulated miRNAs in the Cervical Cancer Progression**

The tumor suppressor miRNA 149 is downregulated in cervical cancer cell lines and tissues. Restoring miRNA-149 expression in vitro inhibits invasion, migration, and proliferation while encouraging cell death. Moreover, overexpression of miRNA-149 prevents the growth of cervical cancer cells in vivo. Focused adhesion, cell migration, and lamellipodia formation are all regulated by the G-protein coupled receptor (GPCR) kinase interacting protein-1 (GIT1). It has been established that miRNA-149 adversely regulates and directly targets GIT1. The PI3K/AKT/mTOR pathway, which is implicated in the process, is negatively regulated by miRNA-149 [65]. The expression levels of miRNA-149 significantly rise at various stages of cervical cancer progression. Particularly, invasive cancer and cervical intraepithelial neoplasia (CIN) 123 increase their expression.

It has been discovered that miRNA-214 functions as a tumor suppressor in cervical cancer. It is downregulated in cervical cancer tissues and its low expression is associated with poor tumor differentiation and advanced tumor stage. Overexpression of miRNA-214 inhibits the proliferation of cervical cancer cells by EZH2 and ARL2 [66] [67]. miRNA214 is significantly elevated during various stages of cervical cancer development. Particularly, invasive cancer and CIN123 cause an increase in its expression [49].

MiRNA-195 is essential for preventing the spread of cervical cancer. Research has demonstrated that cervical cancer cell lines and tissues have a marked downregulation of miRNA-195. Deep stromal invasion, nodal metastases, and advanced cancer stage are all linked to low levels of miRNA-195. Function-wise, miRNA-195 prevents the invasion, migration, and proliferation of cervical cancer cells. Smad3 is one of the several direct targets of miRNA-195 that have been identified [68]. miRNA 195 is significantly elevated during various stages of cervical cancer development. Its expression rises in invasive carcinoma [69] and cervical intraepithelial neoplasia 123.

miRNA-203 has an important role in cervical cancer progression. Studies have shown that miRNA-203 is often downregulated in cervical cancer cell lines and tissues due to promotor methylation [70]. MiR-203 inhibits angiogenesis, cell proliferation, and tumor formation by selectively targeting VEGFA and survivin [7]. There is a significant rise in miRNA-203 during various stages of cervical cancer development. Its expression rises in invasive carcinoma [64] and cervical intraepithelial neoplasia 123.

***Table: 1* The role of miRNA in regulating cell division and apoptosis in cervical cancer and the target genes associated with it.**

|  |  |  |  |
| --- | --- | --- | --- |
| At different stages of cervical cancer, target genes for elevated miRNAs can be identified. | | | |
| All Phases | **miRNA 196a (Foxo1/ p27 kip1)** | | |
| Stage 2,3, and 4 | **MiRNA21 (PDCD4/PTEN)** | **miRNA 155 (LKB1)** | **miRNA 9 (FOXO3/PDCD4)** |
| Stage 3 and 4 | **miRNA 31(ARID1A)** | | |

***Table 2 :* The role of miRNA in regulating the cell division and death of cervical cancer and the target genes associated with it.**

|  |  |  |  |
| --- | --- | --- | --- |
| Downregulated miRNAs and their target genes are seen at various stages of cervical cancer. | | | |
| All Stages | MiRNA-143  (Bcl-2/HIF-1α) | MiRNA-149  (GIT1) | miRNA -203 (VEGFA/Survivin**)** |
| Stage 2,3,4 | SMAD-3 | | |
| Invasive Carcinoma | EZH2/ARL2 | | |

**Conclusion :**

This review highlights the crucial part miRNAs play in the development and spread of cervical cancer linked to HPV infection. As was previously mentioned, high-risk HPV strains change the expression of miRNA, which aids in the development of cervical cancer. By disrupting regular gene regulation and altering cellular miRNA processing machinery, such as DROSHA, HPV encourages carcinogenesis. Serum/plasma, urine, and mucus miRNAs are effective, non-invasive indicators for cervical cancer diagnosis and prognosis. Dysregulated miRNAs, including miR-21-5p, miR-199a-5p, miR-145, and others, exhibit high sensitivity and specificity and provide insight into the progression of the disease and the efficacy of treatment.

When combined with HPV genotype and age, cervical mucus miRNAs increase diagnostic accuracy using complex predictive models. These results demonstrate how crucial miRNAs are to understanding the pathogenesis of cervical cancer and developing targeted diagnostic and therapeutic approaches. Of the miRNAs that were analyzed, miRNA-196a was a noteworthy oncogenic miRNA that was continuously elevated at every stage of cervical intraepithelial neoplasia (invasive carcinoma, CIN1, 2, and 3). Its widespread overexpression highlights its significance for HPV-induced transformation and tumor development. However, the tumor suppressor miRNA-214 was only downregulated at CIN-4 stages, suggesting that it may have a part in the disease's later phases. Previous research demonstrated that certain miRNAs, like miRNA-196a and miRNA-214, serve as accurate indicators of the progression of cervical cancer and that miRNAs are actively regulated at various stages of the disease. The different expression patterns of tumor suppressor miRNAs and oncomiRNAs throughout the stages of CIN underscore their potential for detection and treatment. Notwithstanding these encouraging results, there are still obstacles in converting miRNA-based research into useful medical applications. Further study is needed to understand the molecular interactions of miRNA biomarkers with HPV oncoproteins, verify miRNA biomarkers in larger cohorts, and develop efficacious miRNA-targeting therapeutic strategies. In conclusion, miRNAs have potential for use in clinical settings as cervical cancer biomarkers and treatment agents. Precision medicine and better clinical outcomes for cervical cancer patients are feasible due to their potential as therapeutic targets and biomarkers for early diagnosis.

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Author(s) hereby declare that **NO** generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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