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Review Article

# MicroRNA as Biomarkers for Cervical Cancer

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## Abstract

MicroRNA (miRNA) dysregulation has been found to influence carcinogenesis, metastasis, and the proliferation of human cancers, including cervical cancer. Multiple miRNAs have been shown to impact gene expression, suggesting they have oncogenic or tumor suppressing properties in cervical cancer. This review provides an overview of current knowledge of miRNAs in cervical cancer, and discusses their potential as biomarkers for diagnosis, prognosis and prediction of therapeutic outcomes. miRNAs are very stable and easily collectable from body fluids, and have received attention for use as a candidate specific and sensitive diagnostic/prognostic tool. Research performed over the last decade has shown a substantial number of miRNAs to be dysregulated in cervical cancer. Studies have even identified the target genes and proteins of those miRNAs, furthering our understanding of the impact of miRNA on cellular activity. It is now well known that miRNAs play critical roles in the control of hallmark functions, such as invasion, metastasis, proliferation, and apoptosis, in cervical cancer. Combined with information on dysregulation, this information may help diagnosis at a precancerous state, the prediction of whether cervical cancer cells will go through malignant transformations or migrations, or prognostication. Despite a lack of incorporation in the clinic, miRNAs are gaining interest as biomarkers for cervical cancer.

## Introduction

MicroRNAs (miRNAs) are short strands of noncoding RNA, typically the length of around 22 nucleotides that regulate gene expression [1]. After their influence on gene expression was revealed by Lee, et al. [2] in *Caenorhabditis elegans*, further study has revealed that miRNAs in plants and animals inhibit translation or induce degradation of mRNA to post-transcriptionally regulate gene expression [3]. To date, more than 28,000 mature miRNAs have been identified on miRBase (www.mirbase.org) [4], and as a whole, are estimated to modulate more than 30% of all transcribed genes [3]. Prior studies have found miRNAs to be associated with many cellular processes, such as differentiation, proliferation, apoptosis, and general cell development [5]. Consequently, greater importance has been put on comprehending mRNA regulation mechanisms by miRNA [5]. Recent studies indicate that analyzing dysregulated miRNA expression in various pathological conditions, such as cancer, may help further the understanding of miRNA-induced mRNA regulation mechanisms [5].

Cancer is a complex genetic disease that has been primarily attributed to oncogenes and tumor-suppressing genes [5]. As a result of studies seeking to clarify mRNA regulation mechanisms, dysregulation of countless miRNAs has been discovered in cancer cells, in comparison to normal cells [3], supporting that certain miRNAs can operate as oncogenes or tumor-suppressing genes to inhibit the expression of cancer-related target genes [3]. In addition, Calin, et al. demonstrated that miRNAs expression is dysregulated in many malignancies, and that more than 50% of miRNA genes are located in cancer associated genomic regions or fragile sites [6]. Furthermore, cancer stem cells (CSCs), which propel disease progression, relapse, and resistance to chemotherapy, have radically different miRNA profiles, compared to non-stem cancer cells [4]. These results suggest that miRNAs play a critical role in carcinogenesis and cancer progression.

The potential of miRNA as biomarkers for cancer has been evaluated in various studies and reviews [3,4]. Notably, discovery of specific dysregulated expression has seemed to make way for miRNAs being used as potential diagnostic, prognostic, or therapy-predicting biomarkers [3]. Furthermore, targeting miRNAs and modulating them as a method of cancer treatment is also being investigated [4].

Cervical cancer killed 4,030 women in America alone in 2013 [7], and is widespread across every continent, emerging as a problem to both developed and developing countries [8]. Most cervical

**Table 1**: Upregulated miRNA in cervical cancer carcinogenesis.

| miRNA | Possible target genes | Samples | Technique used | Ref. |
|---|---|---|---|---|
| miR-106a | *PDCD4, MCL1, BCL10, Caspase-7, RBL2* | Tissue | Microarray | [27] |
| miR-106b | | Tissue | Microarray | [27] |
| miR-10a | *CHL1* | Tissue | Microarray | [27,28] |
| miR-1246 | | Tissue | Microarray, RT-PCR | [15] |
| miR-130b | *XIAP, CSF1, MDR1* | Tissue | Microarray | [27] |
| miR-135b | | FFPE | Microarray, RT-PCR | [29] |
| miR-146a | *ROCK1, IRAK1, TRAF6* | Cervical scraping | qRT-PCR | [30] |
| miR-146b-5p | | Tissue | Microarray | [27] |
| miR-155 | *RHEB, mTOR, RPS6KB2, CLDN1* | Tissue | RT-PCR | [20,28] |
| miR-15a | | Tissue | Microarray | [27] |
| miR-15b | | FFPE | Microarray, RT-PCR | [29] |
| miR-16 | | Tissue | Northern blot, qRT-PCR | [31] |
| miR-17 | *c-MYC* | Tissue | Microarray, RT-PCR | [15] |
| miR-181b | | Tissue | qRT-PCR | [32] |
| miR-182 | *ENTPD5, IGFR1, FOXF2, PDCD4* | Tissue | RT-PCR | [33] |
| miR-185 | *DNMT1* | Tissue | Microarray | [27] |
| miR-18a | | Tissue | Microarray | [27] |
| miR-191 | | Tissue | Microarray | [27] |
| miR-192 | *DHFR, p53* | FFPE | Microarray, RT-PCR | [29,34] |
| miR-196 | *HGF* | Tissue | qRT-PCR | [35] |
| miR-196a | | Tissue | Microarray, RT-PCR | [36] |
| miR-200a | *p38α, ZEB1, ZEB2, SIP1* | Tissue | Microarray | [27] |
| miR-200c | *PTEN, TrkB* | Tissue | Microarray | [27] |
| miR-20a | *PTEN, TNSK2* | Tissue | qRT-PCR | [37] |
| miR-20b | | Tissue | Microarray | [27] |
| miR-21 | *PDCD4, PTEN, TPM1, REC, TIMP3, BCL2, CCL20* | Tissue | qRT-PCR | [28,38] |
| miR-224 | | Tissue | qRT-PCR | [39] |
| miR-25 | *ITGAα1, BIM* | Tissue | Northern blot, qRT-PCR | [31] |
| miR-26a | | Tissue | Microarray | [27] |
| miR-27a | *SGPP1, Smad2, Sprout2* | Tissue | Northern blot, qRT-PCR | [31,40] |
| miR-31 | *MET* | FFPE | Microarray, RT-PCR | [41] |
| miR-338 | | Tissue | Microarray | [27] |
| miR-339-5p | | Tissue | Microarray | [27] |
| miR-34c | *p53, CDK6, E2F3* | Tissue | Microarray | [27] |
| miR-378 | | Tissue | Northern blot, qRT-PCR | [31] |
| miR-425 | | Tissue | Microarray | [27] |
| miR-9 | *CDH1, NF-κB, TLN1, RAB34* | Tissue | Microarray | [27] |
| miR-92a | *ITGA5* | Tissue | Northern blot, qRT-PCR | [16] |
| miR-93 | *PTEN* | Tissue | Microarray | [27] |
| miR-944 | | Tissue | qRT-PCR | [32] |
| miR-96 | | Tissue | qRT-PCR | [42] |

**Table 2**: Downregulated miRNA in cervical cancer carcinogenesis.

| miRNA | Possible target genes | Samples | Technique used | Ref. |
|---|---|---|---|---|
| miR-100 | *HOXA1, mTOR, TRIB2, TMEM30A, PLK1, NMT1, CTDSPL, SMARCA5* | Tissue | Northern blot, qRT-PCR | [28,31] |
| miR-101 | *EZH2* | Tissue | Microarray, RT-PCR | [22] |
| miR-125b | | FFPE | Microarray, RT-PCR | [43] |
| miR-126 | *CRK1, PIK3R2, SPRED1, VCAM1* | Tissue | RT-PCR | [44] |
| miR-132 | | Tissue | qRT-PCR | [17] |
| miR-141 | *KEAP1, p38α* | Tissue | Microarray, RT-PCR | [15] |
| miR-143 | *BCL-2, DNMT3a* | FFPE | qRT-PCR | [28,45] |
| miR-145 | *MUC1, IRS1, PXN, OCT, SOX2* | Tissue | qRT-PCR | [28,46,47] |
| miR-148a | | Tissue | Microarray | [27] |
| miR-149 | | Tissue | Microarray | [27] |
| miR-182 | *ENTPD5, IGFR1, FOXF2, PDCD4* | Tissue | qRT-PCR | [48-50] |
| miR-193b | *ARHGAP19, CCND1, ERBB4, KRAS, MCL1* | Tissue | Microarray | [27] |
| miR-195 | *CDKN2A, NF2, JUN* | FFPE | Microarray, RT-PCR | [29] |
| miR-199a | *BCL6, E2F1, IKKB, mTOR, CD44*$^{+}$ | Tissue | Microarray | [27] |
| miR-199b | | FFPE | Microarray, RT-PCR | [29] |
| miR-203 | *ABL1* | Tissue | Microarray, RT-PCR | [15] |
| miR-210 | *K-RAS, BCL-2* | Tissue | Microarray | [27,46,51] |
| miR-212 | *MnSOD* | Tissue | qRT-PCR | [17,52] |
| miR-218 | *ROBO1, BIRC5, LAMB3, GJA1, mTOR* | FFPE | Microarray, RT-PCR | [28,53] |
| miR-218 | *ROBO1, BIRC5, LAMB3, GJA1, mTOR* | Tissue | qRT-PCR | [28,54] |
| miR-26a | | Tissue | qRT-PCR | [55] |
| miR-29a | *YY1* | Tissue | Northern blot, qRT-PCR | [28,31] |
| miR-29c | | Tissue | qRT-PCR | [56] |
| miR-34a | *NOTCH1, JAGGED1,p18Inck4c CDK4, CDK6, Cyclin E2, E2F1, E2F3, E2F5, BCL2, BIRC3, DcR3* | Tissue | qRT-PCR | [28,43] |
| miR-375 | *SP1* | Tissue | Microarray | [28,57] |
| miR-376a | | FFPE | Microarray, RT-PCR | [27] |
| miR-424 | | FFPE | Microarray, RT-PCR | [29] |
| miR-494 | | Tissue | Microarray | [27] |
| miR-497 | *IGF1R* | Tissue | qRT-PCR | [58,59] |
| miR-506 | | Tissue | qRT-PCR | [19] |
| miR-572 | | Tissue | qRT-PCR | [60] |
| miR-617 | | Tissue | Microarray | [27] |
| miR-7 | *XIAP* | Tissue | qRT-PCR | [28,61] |
| miR-99a | *HOXA1, mTOR, TRIB2* | Tissue | Microarray | [28,62] |

cancers are caused by infection with type 16 and 18 high-risk Human Papilloma Virus (HPV) [9]; nevertheless, HPV alone is not sufficient to inducing cervical carcinogenesis: the interaction of two viral-encoded oncoproteins, E6 and E7, with cellular tumor suppressor proteins, dysregulated host proteins, and miRNAs are needed to induce cancer progression [9]. In other words, miRNAs directly influence the oncoproteins that greatly impact cervical cancer cells due to the gene regulating nature of miRNAs and their interactions with cervical cancer oncoproteins. Consequently, many studies have been performed on the relationship between miRNA and cervical cancer, investigating the target genes of individual miRNAs, dysregulation, etc. In this review, we will overview recent discoveries in the field of cervical cancer study regarding miRNAs and their potential as biomarkers for diagnosis, prognosis, and therapy prediction.

## Potential of miRNAs as cervical cancer biomarkers

Although several risk factors have been identified, effective screening Papanicolaou (Pap) method exist [10] and treatments (surgery and/or radiation) are available, cervical cancer still is a major problem especially in developing countries due to the lack of screening and proper treatment [11]. Screening has been relatively successful in developed countries, but early diagnosis of cervical

cancer has not been entirely successful [11]. Cervical cancer has several morphological appearances, molecular features, behaviors, and responses to therapy, which further complicate the detection and treatment of cervical cancer [7].

The currently used methods for screening of cervical cancer are Pap smear and high-risk HPV test. Pap smear tests show poor performance because of low sensitivity and high inter-observer variability. Although high-risk HPV test allows for increased sensitivity, specificity is a problem because only 10% of patients with HPV infection develop cervical cancer. Thus, many women undergo additional unnecessary procedures, such as colposcopy, additional Pap smears, or cervical biopsies [10]. Hence, despite partial success, efforts to improve early detection has been plagued by problems of over diagnosis, inadequate specificity of individual markers, low compliance and a lack of analytical tools for discovering new detection methods [10]. Advanced technologies have led to discoveries of multiple potential biomarkers for cancer. In cervical cancer, the followings have been explored; squamous cell carcinoma antigen, serum fragments of cytokeratin, carcinoma embryonic antigen, and soluble CD44, none of which has shown enough promising results to be applied in the medical field [12]. In cervical cancer, given the long transit time from epithelial atypia to invasive cervical cancer, there are excellent opportunities for the application of effective biomarkers [12].

More predictive or prognostic biomarkers are needed to guide for more effective treatment. Due to the many types of treatments available for different stages of cervical cancer, general prognosis and predicting outcomes for different therapies have also become important issues. Surgery, radiation and chemotherapy alone or in combination are effective in cervical cancer, and several minimal destructive treatments are available, although prognoses are poor upon recurrence. However, there also is a lack of a means for effective determination of appropriate therapy, largely due to inconsistent use of biomarkers and a lack of clinical data [10].

Regarding the potential for miRNAs as cancer biomarkers, a previous study by Manzo-Merino, et al. showed that miRNA tumor profiles are informative, reflecting the developmental lineage and differentiation state of tumors [13]. Subsequently, further studies suggested that miRNAs are important players in the regulation of cellular processes, such as apoptosis, cell cycle progression, metastasis and radio resistance. In cervical cancer, 70 miRNAs have been found to be significantly differentially expressed [8]. Although not all signaling pathways and target proteins have been identified, there is no doubt that miRNAs play a tremendous role in cervical cancer, ranging from carcinogenesis to its continuous development [10]. Another useful characteristic of miRNA is that miRNAs are very stable in bodily fluids and can be detected in serum, plasma, saliva, and urine, among other fluids. In particular, serum miRNAs display great potential to detecting and monitoring cancer progression [14,15]. These features suggest that miRNAs may satisfy current clinical needs for a simple, affordable, and clinically accessible molecular biomarker for diagnosis, prognosis, and prediction of therapeutic outcomes in cervical cancer.

## miRNAs dysregulated in cervical cancer

Prior studies have investigated the specific dysregulations, functions, and target genes of miRNAs in cervical cancer. Several upregulated or downregulated miRNAs are listed in Table 1 & 2 and a meta-analysis on this issue was recently performed [9].

Many target proteins of mRNA are also known, further increasing the potential use of such miRNAs in therapeutic or prognostic applications. Looking at the impacts of miRNAs on cervical cancer, we noted four major influences: general cancer proliferation, metastasis, tumor suppression/oncogenic function, and apoptosis. miRNAs generally target more than one gene; nevertheless, this review will cover miRNAs that show significant dysregulation and have strong correlation to a certain effect on cervical cancer cells.

Regarding general proliferation of cervical cancer cells, it was observed that upregulation of miR-15a, 215b, 216, and 220a causes cell proliferation, invasion and metastasis. Also, the downregulation of miR-299b, 2497, and 2617 has been found to affect the levels of *WNT5A, FZD1, FAS, MYC*, and *FZD6*, which also resulted in further cell proliferation and invasion in cervical cancer [9]. Downregulated miRNAs that affected the transcripts were miR-125b, 2195, 2196a, 199a, and 376c, which upregulated the known transcripts for cell proliferation, including *CDKN2A, CCNE1, CCNE2, E2F3, RARB,* and *IGFBP3*. These actions of miRNAs lead to disruption in cell cycles [9]. A specific miRNA that has been identified as an oncomir with a corresponding protein is miR-92a. Negatively correlated with *FBXW7* in cervical cancer tissues, miR-92a was found to be upregulated, silence *FBXW7*, and act as an onco-miRNA, thereby potentially contributing to the progression and invasiveness of cervical cancer [16].

Metastasis, a crucial step for progression to more severe disease, is also largely impacted by miRNAs. miR-212 and 132 are downregulated in cervical cancer, leading to SMAD2 overexpression that helps the G1/S phase transition of the cell cycle and epithelial to mesenchymal transition [17]. Similarly, the downregulation of miR-1 and 199a and upregulation of miR-200 also impact epithelial mesenchymal transition by disturbing cytokine receptor interactions [9]. In addition, a typically downregulated miR-126 was also discovered to have a tumor metastatic suppressor function in cervical cancer [18]. Among miRNAs that hold correlation in large groups, miR-20a, 296, 2101, 2142, 2944 and let-7f-5p have all been shown to be involved in lymph node metastasis and vascular invasion [9].

Since cervical cancer is a disease that is primarily driven by HPV genes and oncogenic proteins, some miRNAs interact with viral sequences. Namely, upregulation of miR-143 was discovered to increase the oncogenic effects of the HPV16 genes E6 and E7; it also induces ERK5 activity, which would lead to lower cell growth and carcinogenesis in cervical cancer [7]. Also, miR-1, 299b, 2126, 2140, 2196a, 2199a, 2218, and 2497 affect Mitogen Activated Protein Kinase (MAPK) signaling to stimulate malignant transformation [9]. Furthermore, miRNAs can interact with each other, leading to a domino effect of dysregulation: for example, miR-203 acts as a tumor suppressor, and affects others by leading to upregulation of oncogenic miRNAs and other oncogenes [10].

Lastly, miRNA-mediated cellular apoptosis to suppress tumor proliferation, migration, or invasion has received attention as a potential tool for therapy. For instance, miR-21 was discovered to be upregulated in cervical cancer cells and inhibit the expression of tumor-suppressor gene programmed apoptosis [7]. As for miR-506, it is downregulated to prevent cell cycle arrest at the G1/S transition and

**Table 3**: miRNAs as potential diagnostic biomarkers.

| Dysregulation | miRNA annotation |
|---|---|
| Upregulated | miR-25-5p, miR-10a-5p, miR-186a-5p, miR-92a-3p, miR-16-5p |
| Downregulated | miR-29a, miR-99a-5p, miR-199a-3p, miR-218-5p, miR-34a, miR-100-5p, miR-203 |

lowers apoptosis and chemosensitivity of cervical cancer cells. Gli3, a hedgehog pathway transcription factor, is targeted by miR-506 to stop the arrest of cell growth and proliferation, thus decreasing the general number of cells [19]. Similarly to this miRNA, downregulation of miR-155 was shown to prevent apoptosis and induce cell cycle arrest in HeLa and SiHa cells [20]. It was suggested that since protein LKB1 had a direct relationship with miR-155 expression, miR-155 regulates LKB1 expression to further regulate cellular apoptotic activity [20].

These studies have revealed interesting tendencies, such as the impact of miRNAs on each other and a feedback relationship between miRNA and proteins. The identification of target genes or proteins has proven to be quite helpful in clarifying cellular mechanisms. Hence, many scientists have a positive outlook toward using miRNAs as biomarkers. This review will now discuss recent analyses performed on this possibility and how the properties of miRNAs make them appropriate as a cervical cancer biomarker candidate.

## miRNA as biomarkers of cervical cancer diagnosis

As of now, the potential areas for use of miRNA as biomarkers include use as a diagnostic tool and a prognostic tool. In terms of cervical cancer diagnosis, the main challenge lies in determining whether a HPV infection will develop into cervical cancer [21]. As previously illustrated, Pap smears lacks sensitivity, and most importantly, are inconvenient. The need for a sensitive, specific, and convenient diagnostic test has led to many investigations to study dysregulated miRNAs. One of the specific miRNAs that have been determined to have diagnostic value is miR-101. Its expression is significantly reduced in precancerous lesion, and this downregulation stays consistent even through the later stages of cervical cancer [22]. In addition to miR-101, it has been reported that miR-29a and miR-200a can have an application in diagnosing cervical cancer at an early stage, even in precancerous lesions [23]. Furthermore, miR-200 and miR-9 were discovered to act as somewhat of a master regulator in cervical cancer, because they affect the expression levels of multiple genes, miRNAs, and proteins. This property allows them to also be of use as a diagnostic tool, as they will be most definitely dysregulated in cervical cancer [9]. Apart from individual miRNAs that hold diagnostic potential, a set of miRNAs may be more accurate and sensitive for diagnostic usage. Serum miR-21, 29a, 25, 200a and 486 may serve as non-invasive, accurate biomarkers for the diagnosis of cervical cancer [23]. The reasoning behind this is that five miRNAs, compared to the control, was clearly upregulated by an average of 1.8-fold in patients with Cervical Intraepithelial Neoplasia (CIN), the precancerous lesion of cervical cancer for which Pap smear is inefficient in detecting. The study also showed that this test using a combination of five miRNAs is more specific and sensitive than any single miRNA-based assay, SCC antigen, and CA125 [23]. Furthermore, there are 12 miRNAs dysregulated in all steps of precancerous lesion development (Table 3) [9]. Whether the combination of 12 consistently dysregulated miRNAs is helpful in diagnosis should be investigated. Therefore, although no specific, standard diagnostic test using miRNAs has been developed, there is a great possibility thereof.

## miRNAs as biomarkers for cervical cancer prognosis and prediction of therapeutic outcomes

Prognosis, or predicting cervical cancer progression, is more complicated than diagnosis. In addition, treatments are often dependent on them; prognosis carries importance in not only choosing therapeutic strategies but also making follow-up plans. One dimension of prognosis is staging of cervical cancer. One way of dividing precancerous lesions during their development is CIN 1, 2, and 3, prior to progression to cervical cancer. While precancerous lesions can be cured, even through fertility-sparing surgery, cervical cancer requires various treatments and therapies to increase the chance of patient survival. Previous studies showed different miRNA dysregulations in these different stages. Generally, as cervical cancer progresses, more miRNAs are dysregulated, and those that are already dysregulated in a previous stage remain dysregulated [9]. Table 4 lists the stages at which miRNAs are dysregulated. Fast and convenient determination of stage, depending on which miRNAs are dysregulated, will aid in the prognosis of cervical cancer patients, and help doctors decide on a therapeutic strategy [9]. Adding on to the accuracy of this study, another study looked into miRNAs dysregulated in the late stage of cervical cancer. Of those, miR-10a-5p and miR-21-5p were found to perturb the control of apoptosis and cell migration by negatively targeting *SERPINE1, SERPINB5,* and *CHL1* [9]. In addition to these steps, another important part in cervical cancer progression is lymph node metastasis. Extensive study on miRNAs have discovered multiple miRNAs and their target proteins that go through extremely different expression level changes

**Table 4**: Dysregulated miRNAs in cervical cancer and precursor tissues.

| Disease category | Newly upregulated miRNAs | Newly downregulated miRNAs |
|---|---|---|
| CIN 2 | let-7d, miR-338, miR-200a, miR-192, miR-181b, miR-146a, miR-135b, miR-9, miR-15, miR-18a, miR-20b, miR-21, miR-34c, miR-425, miR-339, miR-200c, miR-196a, miR-185, miR-146b, miR-133b, miR-130b, miR-93, miR-155 | miR-125b, miR-375, miR-494, miR-617, miR-149, miR-195, miR-376a, miR-497 |
| CIN 3 | Unknown | miR-376c |
| Cervical cancer | miR-944, miR-200b, miR-189, miR-96, miR-20a, miR-224, miR-31, miR-142, miR-1246, let-7f | miR-99b, miR-196b, miR-1, miR-126, miR-140 |
| Lymph node metastasis | miR-490, miR-323, miR-675, miR-657, miR-551a, miR-550a, miR-1291, miR-328, miR-326, miR-489, miR-585, miR-1184, miR-639, miR-488, miR-612, miR-1204, miR-206 | miR-652, miR-144, miR-96, miR-135b, miR-181d, miR-377, miR-30a, miR-93, miR-30c, miR-126, miR-455, miR-1285, miR-210, miR-191 |

CIN; cervical intraepithelial neoplasia

in transformed lymph nodes [18]. These are outlined in Table 4. Testing a patient specifically for these miRNAs will most likely lead to the detection of dysregulations that give information on the phase or the stage of a patient's cervical cancer, facilitating prognosis.

Another approach towards prognosis is to look at the functions of each dysregulated miRNA and then determine their impact on cellular mechanisms. So far, tremendous amounts of data on the function of dysregulated miRNAs in cervical cancer have been presented. For example, miR-200a has been found to affect the regulation of cell adhesion and distant metastasis the most and to also impact the formation of structures involved in morphogenesis. As mentioned above, this happens as the miR-200 family inhibits epithelial to mesenchymal transition by targeting E-cadherin transcriptional repressors *ZEB1* and *ZEB2*. As cell adhesion and morphogenesis are crucial to the metastatic potential of cancer cells and their migration to distant sites, miR-200a expression levels can indicate whether a cancer will spread through the body or not [24]. Similarly, molecular regulatory machinery miR-494 has been shown to inhibit Pttg1 expression by inhibiting *Pttg1* mRNA expression. Pttg1 increases cervical cancer cell metastasis, and early cancer metastasis leads to poor outcomes, even after resection of the primary cancer, which means that miR-494 levels may be of us determining cervical cancer metastasis risk and help in appropriate therapy or treatment selection [25]. Another interesting dysregulation was miR-9 upregulation, which is related to tumor cell metabolism. The maintenance of high metabolic rate is important for proliferation of cervical cancer cells. Consequently, miR-9 levels can potentially indicate whether a cervical cancer will rapidly proliferate, giving prognostic information about the activeness of the cervical cancer cells [24]. In terms of survival data, upregulation of miR-21 has been associated with poor survival in cervical cancer patients [26]. Indeed, actual clinical data regarding histology and survival rates for patients with certain miRNA dysregulation is lacking for real-life prognosis. Even so, as illustrated above, there is logical experimental evidence that miRNA expression levels are often correlated with cervical cancer development. Hence, miRNAs may be of use as a biomarker for prognosis of cervical cancer, assuming enough clinical data has been gathered.

## Conclusion and Future Perspective

miRNAs, when first discovered, changed the perspective on cellular activities. Due to their nature of influencing countless genes and proteins, many scientists believe that miRNAs can play a crucial role in pathogenesis, specifically for cancer. In addition, studies have suggested that miRNAs may hold advantages over other biomarker as a single miRNA may be tightly controlled due to their widespread influence of up to several thousands of genes, giving increased specificity. Furthermore, as previously mentioned, miRNAs have the advantage of being very stable in bodily fluids, indicating that collection and testing can be done more accurately and quickly.

Currently, the study of miRNAs in cervical cancer has focused on dysregulation itself, finding countless dysregulated miRNAs. More recently, studies have placed attention on diagnosis and prognosis using these new micromolecules, and this review sought to give an overview of where biomarker study on miRNA in cervical cancer stands. Using the dysregulations of miRNAs, diagnosis and prognosis in clinical settings using miRNAs as a biomarker seem extremely probably, especially if further study and data collection is done to establish direct statistical connections between cervical cancer progression and miRNA dysregulation. Thus, miRNAs are being considered as a strong candidate for future cancer biomarkers.

Even with their positive qualities, miRNAs have multiple obstacles to overcome in order to serve as therapeutic targets. One concern that has been expressed is that miRNAs have just been recently discovered, and disruption of miRNA expression may have far more detrimental consequences than what scientists have initially concluded. This is due to the likely complex construct of miRNA: chemotherapeutic agent interactions. Also, existing studies have only been conducted *in vitro* or by using xenograft animal models. There is a lack of evidence that humans can tolerate these newly developed treatments or miRNA application in chemotherapy. Due to these reasons, more attention should be placed on validating the safety and efficiency of miRNA usage in cervical cancer diagnosis, prognosis, and treatment.

## Conflicts of Interest

Dr. Joon-Yong Chung is a member of the Editorial Board of the Journal but the manuscript underwent the same review process like other manuscript. The authors declare that there is no conflict of interest.

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