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Review / Artículo de revisión

Long Non-Coding RNA as Biomarkers in Cervical Cancer: New Perspectives in Diagnosis, Prognosis, and Personalized Treatment

RNA Largos No Codificantes como biomarcadores en cáncer cervicouterino: nuevas perspectivas en diagnóstico, pronóstico y tratamiento personalizado

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ABSTRACT

Long non-coding RNAs are molecules involved in multiple cellular processes and are notable for their functions in various types of cancer. Some of their mechanisms of action include regulating transcription and translation, as well as the activity on functional proteins. This review examines current biomarkers and the potential of the most relevant long non-coding RNAs in cervical cancer, including their diagnostic and therapeutic applications, to promote their incorporation into clinical practice. Long non-coding RNAs show high expression in bodily fluids and cervical tissue of patients with this neoplasm, making them promising biomarkers for early detection, prognosis, and tumor monitoring. Specifically, the long non-coding RNAs PICART1, STARD7-AS1, and PTENP1 are associated with a favorable prognosis by inhibiting tumor growth. In contrast, HOTAIR, MALAT1, and ZFAS1 are involved in cellular processes such as proliferation, migration, and tumor invasion, which are associated with unfavorable prognoses. The high specificity of non-coding RNAs for diagnosis, as well as their potential for targeted and personalized therapies, could revolutionize oncological medicine, enabling more effective treatments with lower toxicity for patients with this type of cancer.

KEY WORDS: Long non-coding RNAs, cervical cancer, biomarker, tumoral progression, prognosis

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RESUMEN

Los RNA largos no codificantes son moléculas involucradas en múltiples procesos celulares y destacan por sus funciones en diferentes tipos de cáncer. Algunos de sus mecanismos de acción son la regulación de la transcripción y traducción, así como su actividad sobre proteínas funcionales. Esta revisión explora los biomarcadores actuales y el potencial de los RNA largos no codificantes más relevantes en cáncer cervicouterino, incluyendo sus aplicaciones diagnósticas y terapéuticas para fomentar su incorporación en la práctica clínica. Los RNAs no codificantes muestran una alta expresión en fluidos corporales y tejido cervical de pacientes con esta neoplasia, posicionándolos como biomarcadores prometedores para la detección temprana, el pronóstico y monitoreo de este tipo de tumores. Específicamente, los RNA largos no codificantes PICART1, STARD7-AS1 y PTENP1 están relacionados con un pronóstico favorable al inhibir el crecimiento tumoral; en contraste, HOTAIR, MALAT1 y ZFAS1 están implicados en procesos celulares de proliferación, migración e invasión tumoral, asociándolos con pronósticos desfavorables. La alta especificidad de los RNA no codificantes en el diagnóstico, así como su potencial en las terapias dirigidas y personalizadas podrían revolucionar la medicina oncológica, permitiendo tratamientos más efectivos y con menor toxicidad para las pacientes con este tipo de cáncer.

PALABRAS CLAVE: RNA largo no codificantes, cáncer cervicouterino, biomarcador, progresión tumoral, pronóstico.

Introduction

Cervical cancer (CC) is a significant public health issue, ranking fourth among the most common types of cancer in women worldwide and representing one of the leading causes of cancer-related mortality among women in countries with developing economies (Bray *et al*., 2024; INEGI, 2025). Persistent infection with high-risk human papillomavirus (HPV) genotypes, such as types 16 and 18, is the primary etiological factor (Álvarez-Aldana *et al*., 2012; Fani *et al.,* 2020; Serrano *et al.,* 2018). Despite advances in detection methods such as cytology, colposcopy, and molecular testing for this virus, limitations in early detection and diagnostic resources remain a challenge, especially in early stages where symptoms are minimal or nonexistent (Hall *et al*., 2018; Maver & Poljak, 2020). Regarding treatment, surgery in early stages and cisplatin-based chemoradiotherapy in advanced stages constitute the therapeutic pillars; however, recurrence and chemoresistance rates emphasize the need for more effective and personalized approaches (Bhatla *et al*., 2019, 2021; Rajaram & Gupta, 2021).

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In this context, long non-coding RNAs (lncRNAs) are emerging as promising tools in CC research due to their roles in regulating essential biological processes, including proliferation, migration, invasion, and treatment resistance. These lncRNAs, whose expression may be altered in CC, have demonstrated both oncogenic and tumor-suppressive roles, positioning them as potential biomarkers for diagnosis, prognosis, and personalized treatment (Patel *et al*., 2025; Wen *et al*., 2025). Therefore, this review compiles novel information on key lncRNAs involved in the development and progression of CC, thereby strengthening scientific evidence on the molecular mechanisms underlying cancer. Furthermore, it seeks to promote their dissemination, update knowledge on emerging biomarkers, and highlight the challenges and perspectives that position them as possible biomarkers with potential clinical application.

Current Landscape of Cervical Cancer

CC is the fourth most common tumor in women worldwide and represents the second leading cause of cancer-related death among Mexican women aged 20 to 60 years (Bray *et al*., 2024; INEGI, 2025). The primary etiology of this type of cancer is HPV infection. It is estimated that 99.7 % of cervical carcinomas are associated with high-risk infections, particularly genotypes 16 and 18, which act through the E6 and E7 proteins to inhibit the tumor suppressors p53 and pRB, promoting genomic instability and malignant transformation (Walboomers *et al*., 1999; Álvarez-Aldana *et al*., 2012; Floudas *et al*., 2025; Pavelescu *et al*., 2025). However, there are cases of HPV-negative CC, which present a worse prognosis and greater aggressiveness (Baay *et al*., 2001; Lee *et al*., 2022). It is important to note that all cervical neoplasms are usually asymptomatic in their early stages, with clinical manifestations only occurring once the tumor invades adjacent structures (Mattern *et al*., 2022; Mwaliko *et al*., 2021).

For diagnosis, the most common tools include cervical cytology and colposcopy (Instituto Mexicano del Seguro Social, 2011), although in industrialized countries, viral DNA detection is also used—a technique that has proven more effective than traditional cytology (Hall *et al*., 2018; Maver & Poljak, 2020). Diagnostic confirmation requires a biopsy; staging is based on the classification system of the International Federation of Gynecology and Obstetrics (FIGO), which allows for treatment planning based on the clinical stage of the tumor. In early stages, treatment consists of surgery, whereas advanced stages generally require cisplatin-based chemoradiotherapy (Bhatla *et al*., 2019, 2021; Rajaram & Gupta, 2021).

The prognosis of CC is influenced by various factors, such as the patient's age, the presence of metastases, and the response to treatment. Detecting cancer in early stages, as well as HPV positivity, is associated with better clinical outcomes and greater survival (del Campo & Matamoros, 2021; National Institute of Health, 2022). This underscores the importance of effective early detection strategies using biomarkers and timely treatment in the management of this disease.

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Use of Biomarkers for Diagnosis, Monitoring, and Treatment Response in Cancer Patients

The United States National Institutes of Health (NIH) defines the term “biomarker” as a characteristic used as an indicator of normal biological processes, pathological processes, or responses to interventions (FDA-NIH Biomarker Working Group, 2020). In the context of cancer, a biomarker is a specific molecule that indicates the presence, risk, or prognosis of the disease. Biomarkers include genomic, epigenetic, proteomic, cellular, histological, and physiological molecules that play a key role in diagnoFsis, monitoring, and treatment selection (Sarhadi & Armengol, 2022).

Among genetic markers for cancer, mutations in genes such as TP53 (Donehower *et al*., 2019), PIK3CA (Yu *et al*., 2021), and the Rb protein stand out, as well as signaling pathways like NF-κB and mTOR, which influence cellular processes such as cell cycle regulation, signaling, and DNA maintenance (Kandoth *et al*., 2013; Zhou *et al*., 2021a; Rodrik-Outmezguine *et al*., 2016). Proteomic markers such as AFP, CA-125, CEA, and HER2 are also valuable tools for the detection and monitoring of various cancers, from hepatocellular to pancreatic, colorectal, and breast cancer (Feng *et al*., 2021; Kawamura *et al*., 2022; Liu *et al*., 2020; Landegren & Hammond, 2021). In the histopathological field, biomarkers like p16 and Ki-67 help identify cellular changes induced by HPV, improving the diagnostic accuracy of precancerous lesions (Yu *et al*., 2022).

Immune checkpoints also represent important biomarkers for targeted cancer therapies. Molecules such as PD-L1, CTLA-4, TIM-3, LAG-3, and TIGIT have proven to be effective targets for chemotherapy by blocking immune suppression and reducing tumors (Zhou *et al*., 2024; Huang *et al*., 2023; Cai *et al*., 2023). In addition, innovative biomarkers such as circulating tumor DNA (ctDNA) allow for non-invasive disease monitoring, while microRNAs (miRNAs, miRs) and lncRNAs are emerging as promising tools in diagnosis, prognosis, and therapeutic response (Taniguchi *et al*., 2021; Kapranov *et al*., 2007). Integrating these biomarkers into clinical practice is essential for advancing oncology care towards being more personalized and effective.

Long Non-Coding RNA (lncRNA): General Characteristics and Biological Functions

LncRNAs are a class of long nucleic acids with 200 or more nucleotides in length. They are part of the non-coding genetic material, which comprises between 65–75% of the entire genome (St. Laurent *et al*., 2015).

They are deregulated in various types of cancer, including colorectal, hepatocellular, breast, ovarian, and lung cancer, among many other malignant tumors (Zhang, 2024). Deregulation and mutations in lncRNAs are significantly involved in tumor pathogenesis. Changes or mutations in the expression levels of specific lncRNAs can lead to tumor growth or metastasis, exhibiting both oncogenic and tumor-suppressive activities (Schmitz *et al*., 2016).

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LncRNAs play numerous roles in a variety of biological processes, particularly through their function as endogenous competing RNAs (ceRNAs) or natural sponges for miRNAs. For example, HOTAIR is an lncRNA that represses miRNA-214-3p expression (Figure 1a). By containing specific binding sites, lncRNAs can influence the expression of target gene miRNAs by sequestering them and blocking their interaction with the corresponding targets (Gao *et al.,* 2020; Sweta *et al*., 2019; Zhou *et al*., 2021a).

One of the lesser-known functions of lncRNAs is their ability to participate in the generation of other smaller and functional RNA types (Matouk *et al*., 2014; Matouk *et al*., 2016). For instance, some so-called “mirtrons” derive from splicing fragments during RNA maturation and, once released, become miRNAs with important regulatory functions (Berezikov *et al*., 2007). There are also lncRNAs that function as precursors to entire clusters of miRNAs, such as the miRNA-17–92 cluster, which originates from a single lncRNA (Figure 1b) (Lee *et al*., 2003; Chen *et al*., 2020).

Additionally, they could regulate various essential genetic processes, including transcription, translation, imprinting, and genome rearrangement, which positions them as key elements in genetic control. An example is WT1-AS, which acts on the transcription of the WT1 gene involved in the development and maturation of gastric cancer stem cells (Figure 1c) (Zhang *et al*., 2023). Similarly, the lncRNA PICART-1 promotes the expression of the TCF21 protein, which inhibits angiogenesis and suppresses tumor growth in different types of cancer (Figure 1d) (Duan *et al*., 2019; Sweta *et al*., 2019).

Likewise, lncRNAs interact with various proteins, modulating their assembly, binding site, and function (Figure 1e). In this context, the lncRNA PTENP1 acts as a promoter of the PTEN protein, one of the most important tumor suppressor proteins. They also serve as scaffolds for molecular complexes such as the Polycomb Repressive Complex 2 (PRC2), which participates in chromatin remodeling and gene silencing, contributing to epigenetic regulation (Fan *et al*., 2020; Schmitz *et al*., 2016).

Finally, lncRNAs play a crucial role in biological mechanisms such as apoptosis and other forms of cell death. They actively participate in the regulation of histone modifications and chromatin state, directly influencing the structure and function of the genome, as in the case of HOTAIR, which regulates histone methylation (Figure 1f). Figure 1 summarizes the main cellular and molecular mechanisms of lncRNAs and some of their specific molecular targets in cancer (Sweta *et al*., 2019; Trujano-Camacho *et al*., 2024).

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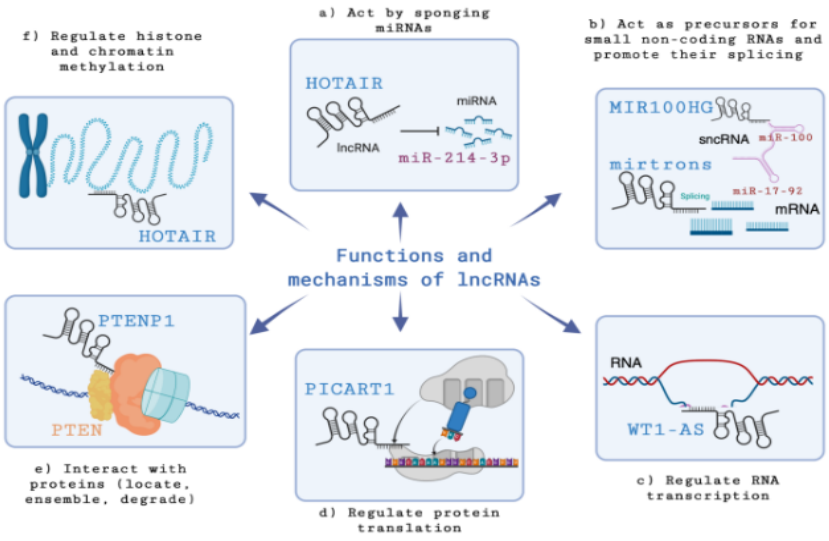

Figure 1. Functions and mechanisms of lncRNAs.

This diagram highlights the main roles of lncRNAs: (a) acting as miRNA sponges, such as HOTAIR with miR-214-3p; (b) serving as precursors to small RNAs or micro RNAs, such as mirtrons and MIR100G; (c) regulating transcription, such as WT1-AS; (d) modulating protein translation, like PICART1; (e) interacting with proteins to influence their function, like PTENP1; and (f) regulating histone and chromatin methylation, like HOTAIR.

Source: Created by the authors using BioRender.com.

Types of Long Non-Coding RNA (lncRNA)

There are multiple types of lncRNAs, which can be classified according to their size, association with protein-coding genes, association with DNA elements, repetitive sequences, stability, biochemical nature, or their functions in different cellular processes. Below, *Table 1* presents the two most commonly used classifications: by size and association with protein-coding genes (St. Laurent *et al.*, 2015).

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Table 1. Classification of lncRNA by Size and Protein Association1

Classification	Name	Abbreviation	Examples
Transcript size	Long non-coding RNA	LncRNA	
	Intragenic long non-coding RNA	lincRNA	-LINC00449 -LINC01270 -HOTAIR -RNA-p21 - LINC00015
	Very large intragenic long RNA	vlincRNA	- VAD - BCLIN5
	Macro RNA	-	- HOTAIR - XIST - MALAT1
	Promoter-associated long RNA	PALR	- PVT1
Association with protein-coding genes	Intronic non-coding RNA	sisRNA,TIN, PIN	- H19 - NEAT1 - COLDAIR
	Circular intronic RNA	ciRNA	- ciRS-7
	Sense non-coding RNA	Sense ncRNA	- HOTAIR
	Natural antisense non-coding RNA	asRNA, NAT	- ANRIL
	Antisense mirror	-	- p15AS - MALAT1 - Uchl1-AS
	Exonic circular RNA	ecircRNA	- circRNA-100284 - circHIPK3
	Chimeric RNA	-	- KCNQ1OT1

Modified from: (St. Laurent *et al*., 2015; Statello *et al*., 2021; Chodurska & Kunej, 2025)

Long Non-Coding RNAs Related to Cervical Cancer Progression

Numerous lncRNAs play a crucial role in the pathophysiology, progression, metastasis, and treatment resistance of cervical cancer (CC). As mentioned earlier, lncRNAs act through interactions with other genes, such as miRNAs, thereby modulating their functions and inducing changes in the disease's pathogenesis. Some lncRNAs are classified as "poor prognosis" markers due to their negative impact on the disease course by facilitating processes such as cell proliferation, migration, and invasion, or by contributing to poor treatment response. In contrast, as shown in Figure 2, specific lncRNAs are associated with more favorable clinical outcomes by acting as protective factors that inhibit tumor growth and slow cancer progression (Chi *et al*., 2017).

Due to their tissue-specific distribution, lncRNAs have potential as new biomarkers for

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cancer diagnosis, prognosis, and treatment. This specificity may be particularly useful for tailoring personalized treatment strategies compared to proteins or small RNAs, making them valuable tools in precision oncology (Tornesello *et al*., 2020). Since 2012, research into the specific role of certain lncRNAs has intensified, particularly regarding their interaction with other genes and their impact on cancer development. Studies have used a wide range of methodologies, including cell lines, animal models, cervical tissue, vaginal secretions, blood, and serum samples from patients with cervical neoplasms (Gibb *et al*., 2012; He *et al*., 2020; Wang *et al*., 2023; Lizano *et al*., 2024).

In the context of CC, key lncRNAs have been identified in tumor progression, prognosis, and treatment resistance, positioning them as potential candidates for clinical biomarker use. For example, HOTAIR is a widely studied lncRNA that promotes cell proliferation, migration, and invasion, and is also associated with chemoresistance to agents such as cisplatin, paclitaxel, and docetaxel. Its overexpression in CC cell lines, cervical tissue, and vaginal secretions is linked to worse prognosis in patients with this cancer type (Li *et al*., 2018; Buranjiang *et al*., 2023).

Similarly, MALAT1 plays an important role by promoting proliferation, metastasis, and cisplatin resistance, thereby promoting tumor growth (Arun *et al*., 2020). Its overexpression in circulating serum from CC patients (Naz *et al*., 2021), cell lines, and animal models is also indicative of an unfavorable prognosis (Hu *et al*., 2023; Wang *et al*., 2018; Sun *et al*., 2018). Likewise, ZFAS1 contributes to the progression of cervical tumors by promoting proliferation, migration, and invasion in advanced stages, as well as resistance to cisplatin, with overexpression observed in cervical tissue and cell lines (Feng *et al*., 2019).

On the other hand, some lncRNAs such as PICART1 and STARD7-AS1 are associated with better clinical outcomes due to their inhibitory role in cell proliferation, migration, and invasion. PICART1, which is underexpressed in advanced cancer stages, is associated with a better prognosis by inhibiting key tumor processes (Zhao *et al*., 2020). Similarly, STARD7-AS1 and PTENP1 promote autophagy and are also underexpressed in cell lines and cervical tissue, correlating with improved clinical outcomes (Yin *et al*., 2024).

Table 2 summarizes key lncRNAs in cervical cancer (CC), including their most relevant therapeutic targets, mechanisms of action, expression levels, and associated prognosis. These examples highlight the multiple functions of lncRNAs, which can act as oncogenes or tumor suppressors, underscoring their potential as diagnostic, prognostic, and personalized treatment selection tools.

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Table 2. Main lncRNAs in Cervical Cancer: Molecular targets, biological effects, expression in biological samples, and their prognostic implications.

LncRNA	Target	Mechanism of action	Function	Expression in CC	Prognosis	Reference
SNHG1	miR-195/ NEK2	NHG1 regulates NEK2 by targeting miR-195.	Promotes progression.	Overexpression in cervical tissue.	Poor prognosis Increases proliferation and invasion in cervical cancer tissue (Student's t-test, $P < 0.05$)	(Ji *et al*., 2020)
LINC00324	miR-195-5p	LINC00324 downregulates miR-195-5p.	Promotes proliferation, migration, and invasion.	Overexpression in cervical tissue	Poor prognosis Association with lymph node metastasis ($p = 0.013$) and TNM stage ($p = 0.028$) in patients with cervical cancer (Chi-square test, $P < 0.05$)	(Ni *et al*., 2023)
HOTAIR	miR-331-1p miR -214-3p, and miR-143-3p	Sponges miR-331-3p to promote RCC2 expression. Modulates miR-143-3p to regulate BCL2. Sponges miR-214-3p to promote proliferation and inhibit apoptosis (HPV16+ cells).	Promotes proliferation, migration, invasion, chemoresistance (cisplatin, paclitaxel, docetaxel), and radioresistance.	Overexpression in cell lines, cervical tissue, and vaginal secretion.	Poor prognosis Increases proliferation, migration, and invasion in cervical cancer cells (Student's t-test, $P < 0.01$) Tumor volume and weight in BALB/c mice inoculated with cervical cancer cells (Student's t-test, $P < 0.05$) Diagnostic efficacy in cervical cancer patients vs. healthy women (ROC analysis, 92.7% accuracy in vaginal discharge and 89.3% in serum) Chemoresistance in cervical cancer cells (ANOVA, $P < 0.05$)	(Buranjiang *et al*., 2023; Li *et al*., 2018; Liu *et al*., 2018; Liu & Li, 2023; Zhang *et al*., 2022; Zhou *et al*;, 2021b)

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Table 2. Main lncRNAs in Cervical Cancer: Molecular targets, biological effects, expression in biological samples, and their prognostic implications.

LncRNA	Target	Mechanism of action	Function	Expression in CC	Prognosis	Reference
ZFAS1	miR-190a-3p/KLF6	Sponges miR-190a-3p, leading to upregulation of KLF6 (tumor suppressor).	Promotes proliferation, migration, invasion, advanced FIGO stage, and cisplatin chemoresistance.	Overexpression in cervical tissue and cell lines.	<u>Poor prognosis</u> Proliferation, migration, and invasion in cervical cancer cells ($P < 0.05$) Histological classification and FIGO stage ($P < 0.001$) Chemoresistance in cervical cancer cells ($P < 0.05$) Decreased overall survival (Kaplan–Meier/log-rank test, $P < 0.05$)	(Feng *et al*., 2019; Su *et al*., 2022)
MALAT1	miR-141-3p ALKBH5 miR-145	Sponges miR-141-3p to release the inhibition of ALKBH5. Sponges miR-145 allow expression of tumor suppressor genes (e.g., SMAD3, TGFBR2).	Promotes proliferation, metastasis, and cisplatin resistance, induces tumor growth.	Overexpression in patient's plasma, cell lines, and animal models.	<u>Poor prognosis</u> Cisplatin resistance in cervical cancer patients (ANOVA, $P < 0.05$) Increased proliferation, and inhibition of apoptosis in drug-resistant cervical cancer cells (ANOVA, $P < 0.05$)	(Hu *et al*., 2023; Wang *et al*., 2018; Wu *et al*., 2023)

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LncRNA	Target	Mechanism of action	Function	Expression in CC	Prognosis	Reference
SFTA1P	PTBP1, and TPM4	Interacts with PTBP1 to regulate TPM4 stability.	Promotes proliferation, migration, and invasion of cancer cells.	Overexpression in cell lines, and animal models.	<u>Poor prognosis</u> Proliferation, migration, and invasion in cervical cancer cells ($P < 0.001$) Development of secondary metastases in the pelvic cavity, lungs, and brain in BALB/c mice.	(Luo *et al*., 2022)
PVT1	miR-42	Acts as a ceRNA sponging miR-424.	Promotes proliferation, migration, and invasion.	Overexpression in serum, cervical cancer tissue, and cell lines.	<u>Poor prognosis</u> Proliferation, migration, and invasion in cervical cancer cells (t test, $P < 0.05$)	(Gao *et al*., 2017)
H19	miR-140/ ALDH1A	Regulates the miR-140 / ALDH1A1 axis, inhibiting tumor growth.	Promotes progression.	Overexpressed in cell lines.	<u>Poor prognosis</u> Cell proliferation, apoptosis, migration, and invasion in cervical cancer cells (t test, $P < 0.05$)	(Ming *et al*., 2025)
PICART1	ARID1A/ TCF21	Recruits ARID1A to activate TCF21 expression.	Inhibition of proliferation, migration, and invasion. Better survival.	Underexpression in cervical tissue, especially in TNM stages III, and IV.	<u>Better prognosis</u> Proliferation, migration, and invasion (t test, $P < 0.05$) Survival in patients with cervical cancer (Kaplan-Meier curve, $P < 0.05$)	(Zhao *et al*., 2020)

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Table 2. Main lncRNAs in Cervical Cancer: Molecular targets, biological effects, expression in biological samples, and their prognostic implications.

LncRNA	Target	Mechanism of action	Function	Expression in CC	Prognosis	Reference
STARD7-AS1	miR-31-5p/ TXNIP	Increases TXNIP expression via interaction with miR-31-5p.	Inhibition of proliferation, and promotion of autophagy.	Underexpression in cell lines.	<u>Better prognosis</u> Proliferation ($P < 0.05$) and autophagy ($P < 0.01$) in cervical cancer cells (t test) Prediction of overall survival in patients with cervical cancer (Kaplan-Meier curves using ENCORI software)	(Yin *et al.*, 2024)
WT1-AS	miR-203a5p/ FOXN2	Negatively regulates miR-203a-5p, allowing FOXN2 expression.	Inhibition of growth, migration, and invasion.	Underexpression in cell lines and cervical tissue.	<u>Better prognosis</u> Proliferation, migration, and invasion in cervical cancer cells (t test, $P < 0.01$) FIGO stage, lymph node metastasis in patients with cervical cancer (t test, $P < 0.05$)	(Dai *et al.*, 2019)

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Table 2. Main lncRNAs in Cervical Cancer: Molecular targets, biological effects, expression in biological samples, and their prognostic implications.

LncRNA	Target	Mechanism of action	Function	Expression in CC	Prognosis	Reference
PDHB-AS	miR-45365-5p Wnt7b miR-582-5p	miR-4536-5p inhibits PDHB-AS. PDHB-AS suppresses Wnt7b expression. Also binds miR-582-5p.	Inhibits tumor growth and EMT, increases sensitivity to cisplatin.	Underexpression in cell lines and cervical tissue (animal model).	<u>Better prognosis</u> Migration and invasion in cervical cancer cells (t test, P < 0.01) Prediction of overall survival in patients with cervical cancer (Kaplan-Meier curves using the GEPIA database) Sensitivity to cisplatin (t test, P < 0.01)	(Chi *et al*., 2023)
PTENP1	miR-106b/ PTEN	Competitively binds miR-106b, promoting PTEN expression.	Inhibits cell proliferation and EMT, induces apoptosis.	Downregulated in cell lines and cervical tissue.	<u>Better prognosis</u> Proliferation and apoptosis in cervical cancer cells (Student's t-test, P < 0.01) EMT in cervical cancer cells, increased E-cadherin , and decreased vimentin (Student's t-test, P < 0.05)	(Fan *et al*., 2020)
Linc00887	miR-454-3p/ FRMD6-Hippo	Sponges miR-454-3p to activate FRMD6-Hippo signaling.	Inhibits proliferation and invasion.	Downregulated cervical cell lines and tissue.	<u>Better prognosis</u> Proliferation and invasion in cervical cancer cells (Student's t-test, *P* < 0.05)	(Li *et al*., 2021)

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Current Challenges and Potential Applications of Long Non-Coding RNAs in the Diagnosis and Treatment of Cervical Cancer

Early detection of cervical cancer (CC) remains the most effective method for preventing this disease. Its main objective is to identify high-grade precancerous lesions and invasive cervical cancer in early and asymptomatic stages, while minimizing the detection and unnecessary treatment of transient HPV infections and associated benign lesions (McGraw & Ferrante, 2014). However, current detection methods present significant limitations that hinder their effectiveness. An example is the use of the immunohistochemical marker p16 to classify lesion grade, which shows limitations in distinguishing between low- and high-grade intraepithelial lesions (Safaeian & Sherman, 2013; Liu *et al*., 2022).

Another barrier of existing methods involves the complexity of universal access, as health service disparities are highly prominent in Mexico. This inequality especially affects racial, sexual, and religious minorities, people in rural areas, and individuals with physical or mental disabilities (Fuzzell *et al*., 2021). It is important to note that the discomfort women experience during cervical cytology is a contributing factor to the low rate of early detection. Many patients find these procedures painful, uncomfortable, and invasive, which generates fear and anxiety and hinders the routine use of such tests (Agurto *et al*., 2004; Bukowska-Durawa & Luszczynska, 2014; Peña, 2023). This underscores the need to develop less invasive and more accessible diagnostic methods.

For some time, tumor markers, such as antigens and hormones, have revolutionized modern medicine; however, their limited specificity and sensitivity can lead to diagnostic errors and false negatives. In this regard, lncRNAs are emerging as promising biomarkers for CC detection, using more specific and less invasive methods. Specifically, lncRNAs such as HOTAIR, MALAT1, and MEG3 stand out as diagnostic biomarkers for CC, as their presence has been detected within exosomes derived from cervical lavage or urine samples. This not only facilitates less invasive diagnostics but could also help predict cancer recurrence in women worldwide (Figure 2) (Beylerli *et al*., 2022; Carlevaro-Fita *et al*., 2020; Serghiou *et al.,* 2016; Zhang *et al.,* 2016).

Nonetheless, given the novelty of this therapeutic strategy, several interesting challenges remain to be addressed. Their high expression variability among individuals offers a personalized approach, but it also poses difficulties in classifying lncRNAs across different cancer types and patient profiles (Esposito *et al*., 2022). It is currently estimated that there are between 20,000 and 100,000 identified lncRNA genes, of which only 1,000 to 2,000 have been functionally characterized, leaving 99% unexplored (Ma *et al*., 2019). This gap represents a significant opportunity for future research, especially in high-mortality diseases such as CC.

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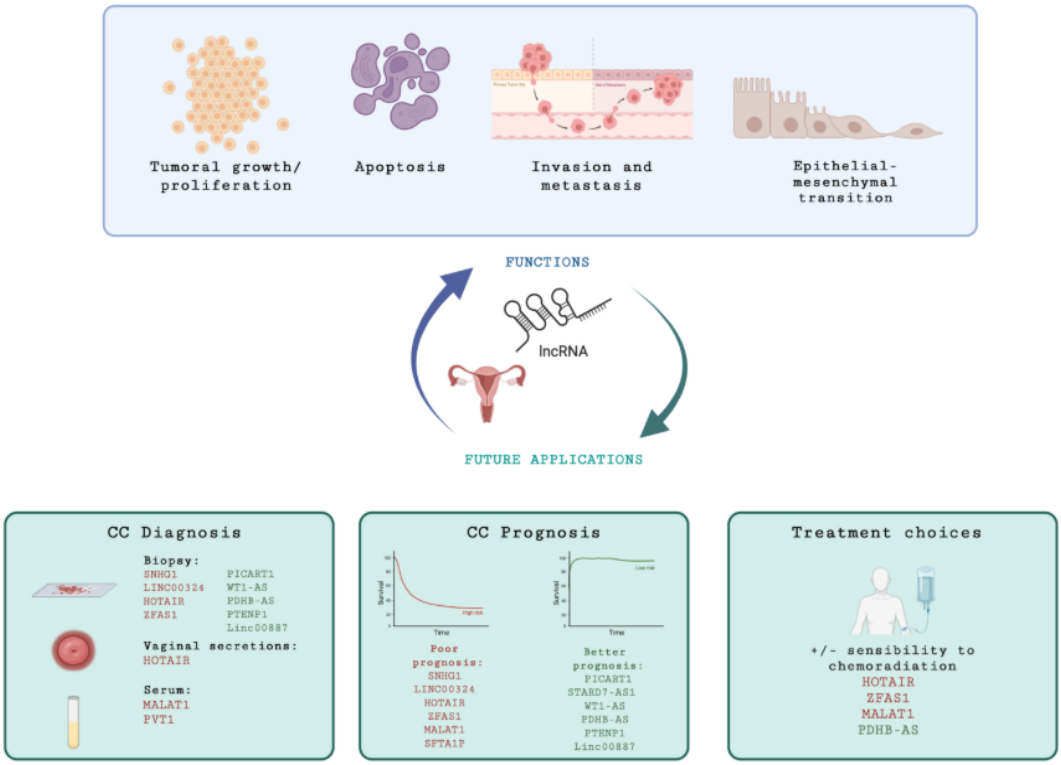

Figure 2. Biological Functions and Future Applications of Long Non-Coding RNAs (lncRNAs).

This figure illustrates the key functions of lncRNAs, including their roles in tumor growth and proliferation, apoptosis, invasion and metastasis, and epithelial–mesenchymal transition. It also highlights their potential future applications in cervical cancer (CC) diagnosis through serum, biopsy, or cervical mucus analysis; in prognosis determination by correlating their expression with better or worse clinical outcomes; and in treatment selection by evaluating sensitivity to radiochemotherapy.

Source: Created by the authors using BioRender.com.

Several technical details in therapeutic delivery strategies still need to be resolved, such as ensuring that lncRNAs reach the tumor site and favorably alter the disease course. In this regard, the use of exosomes to transport intracellular material has shown promise in CC (Huang *et al*., 2021; Wang *et al*., 2023), as well as the implementation of the CRISPR/Cas system and post-transcriptional inhibition using antisense oligonucleotides, which could be useful for treating this cancer (He *et al*., 2020).

Another challenge involves understanding their mechanisms in processes such as functional plasticity and chromatin regulation, as well as their deregulation in cancer and other diseases

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(Mattick *et al*., 2023). Likewise, baseline reference levels of lncRNAs in healthy individuals have not yet been established, and there are currently no regulated protocols for their monitoring and approval as biomarkers, making their use in patients more complex, as most studies remain in the preclinical phase (Aswathy & Sumathi, 2023).

To address these complexities, machine learning may be key to analyzing large volumes of genomic, epigenomic, and transcriptomic data, allowing identification of the relationships and causality of these molecules and their clinical applications (Al Mamun *et al*., 2021; Mattick *et al*., 2023). For example, artificial intelligence using deep learning models is proving to be a highly useful tool to analyze this information, having already succeeded in predicting the relationship between lncRNAs and chemoresistance to antitumor therapies (Aswathy & Sumathi, 2023; Gao *et al*., 2023).

However, implementing these technologies into the medical practice still faces various challenges, including the high cost of genomic medicine, which limits access and highlights the need for cost-effectiveness studies to assess its feasibility for the general population (Gareev *et al*., 2021; Christofyllakis *et al*., 2022). The lack of trained personnel in the field and the underrepresentation of Latin American populations in genomic databases are additional limitations that must still be addressed (Perenguez *et al*., 2024). Their integration into clinical practice requires overcoming these challenges related to functional characterization, economic accessibility, and validation in more robust studies.

To overcome the limitations associated with their integration into medicine, it is crucial to invest in the training of professionals specialized in genomics and bioinformatics and to encourage the inclusion of Latin American and Afro-descendant populations in genomic databases, which will strengthen the validity of the studies. In addition, promoting international collaboration and investment in more accessible and cost-effective sequencing technologies will help expand access to these innovative tools (Coan *et al*., 2024). With the scientific community's commitment and growing public policy support, lncRNAs could revolutionize how we understand and treat various diseases, offering new opportunities for personalized medicine.

Today, the implementation of less invasive diagnostic and prognostic methods for CC is highly relevant. In a context where equity in health access and personalized treatment are global priorities, these advances could make a significant difference in the fight against this disease. Reducing barriers related to the discomfort and fear of traditional procedures may favor earlier and more accurate detection, increasing the chances of timely and effective interventions for patients with CC.

This not only changes the way we approach this neoplasm but also optimizes health system resources, making it more efficient and accessible. In summary, implementing these innovative methods in practice could significantly improve clinical outcomes and the quality of life for patients, marking a major step forward in modern medicine.

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Conclusion

LncRNAs play a crucial role in the regulation of multiple cellular processes, including proliferation, differentiation, and cell death; each of them fundamental in tumor development and progression. In particular, the utility of lncRNAs as biomarkers in cervical cancer (CC) has been extensively demonstrated. The main significance of this review lies in integrating these molecules into clinical protocols. Incorporating lncRNAs into clinical practice would allow prediction of tumor response to certain treatments and the development of specific therapies that target either the RNAs themselves or the pathways in which they are involved.

Most current studies have focused on discovering or understanding the molecular mechanisms of lncRNAs, while few have explored their clinical application or assessed their cost and feasibility. These are precisely the most critical perspectives for the future use of these biomarkers in the diagnosis, prognosis, and treatment of CC. In doing so, it would become possible to develop therapies tailored to the molecular profile of each patient, minimizing side effects and enhancing antitumor effectiveness.

Author Contributions

Conceptualization of the work: B.R.T., V.C.R.G.; Writing and manuscript preparation: B.R.T., V.C.R.G., P.C.O.L.; Drafting, review, and editing: B.R.T., V.C.R.G., P.C.O.L.; Figure creation and editing: B.R.T., V.C.R.G.

Conflict of Interest

The authors declare no conflict of interest.

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