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IDENTIFICAÇÃO DE RNAs LONGOS NÃO CODIFICANTES SNHGs ASSOCIADOS COM FATORES DE PIOR PROGNÓSTICO EM CÂNCER CERVICAL: UMA REVISÃO SISTEMÁTICA DA LITERATURA

ELEILDE ALMEIDA ARAUJO

São Luís
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Dissertação apresentada ao Programa de Pós-Graduação em Saúde do Adulto da Universidade Federal do Maranhão para obtenção do Grau de Mestre em Saúde do Adulto.

Área de Concentração: Processos biológicos em Saúde

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Orientador: Prof. Dr. Marcelo Souza de Andrade

Co-orientador: Profª. Dra. Jaqueline Diniz Pinho

Coordenador: Prof. Dr. Marcelo Souza de Andrade

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A Banca Examinadora da Defesa de Mestrado, apresentada em sessão pública, considerou o candidato aprovado em: ____/____/____.

Prof. Dr. Marcelo de Souza Andrade
Universidade Federal do Maranhão

Profª. Drª. Ana Gabriela Caldas Oliveira
Universidade Federal do Maranhão

Prof. Dr. Gyl Eanes Barros Silva
Universidade Federal do Maranhão

Profª. Drª Maria do Socorro de Sousa Cartagenes
Universidade Federal do Maranhão

Prof. Dra. Juliana Maria Trindade Bezerra
Universidade Estadual do Maranhão

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RESUMO

Introdução: O câncer cervical (CC) é o terceiro tipo de câncer mais incidente entre mulheres, no Brasil e para 2023 foram estimados mais de 17 mil casos, e cerca de 800 no estado do Maranhão. Os fatores de pior prognóstico estão associados a uma menor taxa de sobrevida em pacientes com este tipo de doença. A expressão aberrante de RNAs não codificantes (ncRNAs) tem sido associados a estes fatores, apontando estas biomoléculas como potenciais biomarcadores. Dentre os ncRNAs, destacam-se os RNAs longos não codificantes (lncRNAs), da classe SNHGs (*small nucleolar host gene*), os quais ainda são pouco explorados no CC. **Objetivo**: Identificar SNHGs relacionados com fatores de pior prognóstico em câncer de cervical, através de uma busca sistemática da literatura. **Métodos:** Este estudo foi conduzido de acordo com o protocolo PRIMA-scR, o anagrama Picos, após foi feita a busca literária nas fontes de pesquisa: PubMed, ScienceDirect, Lilacs e Medline, após os critérios de inclusão e exclusão, foram extraídas informações como: nível de expressão, tipo de amostra, técnicas abordadas, função biológica, significado clínico, elementos alvos (microRNAs e vias) regulados pelos SNHGs. **Resultado:** De um total de 3.803 estudos, foram selecionados 12 os quais contemplaram 8 SNHGs, (GAS5, SNHG5, SNHG7, SNHG12, SNHG14, SNHG16, SNHG17 e SNHG20) associados ao CC, todos exceto o GAS5 apresentaram uma superexpressão que foi associada com fatores de pior prognóstico como: proliferação, migração, invasão, apoptose, metástase linfonodal, FIGO e tamanho do tumor, grau de diferenciação no CC. Dos 8 SNHGs estudados, 7 SNHGs (SNHG5, SNHG12, SNHG14, SNHG16, SNHG17, SNHG20 e SNHG2/GAS5) podem atuar como esponjas moleculares de miRNAs. **Conclusão:** No geral, esta família de SNHGs faz parte de uma rede de interação, regulando vias importantes para a carcinogênese. Portanto, podem futuramente serem usados como marcadores biológicos e alvos terapêuticos em suas amplas aplicações no diagnóstico e tratamento, sendo necessárias mais pesquisas para a compreensão do papel dos SNHGs no câncer cervical.

Palavras-Chave: LncRNAs, câncer cervical, SNHG. metástase, biomarcador.

ABSTRACT

Introduction: Cervical Cancer (CC) is the third most common type of cancer amongst women in Brazil. More than 17,000 cases were estimated for 2023, with about 800 of them in the state of Maranhão. Worse prognostic factors are associated to a lower survival rate in patients with this type of disease. The aberrant expression of non-coding RNAs (ncRNAs) has been associated with these factors, pointing to these biomolecules as potential biomarkers. Among the ncRNAs, we highlight the long non-coding RNAs (lncRNAs) of the class SNHGs (small nucleolar host gene), which are still underexplored for CC. **Objective**: To identify SNHGs related to worse prognostic factors in cervical cancer through a systematic literature search. Methods: This study was conducted according to the PRISMA-scR protocol, using the PICO strategy. Then, a literary search was carried out in the following sources: PubMed, ScienceDirect, Lilacs and Medline. After the application of inclusion and exclusion criteria, we extracted information such as: expression level, sample type, techniques addressed, biological function, clinical significance, target elements (microRNAs and pathways) regulated by SNHGs. **Results**: Out of a total od 3,803 studies, we selected 12 that contemplated 8 SNHGs (GAS5, SNHG5, SNHG7, SNHG12, SNHG14, SNHG16, SNHG17 and SNHG20) associated to CC. All, except for GAS5, presented an overexpression that was associated to worse prognosis factors such as: proliferation, migration, invasion, apoptosis, lymph node metastasis, FIGO and tumor size, degree of differentiation in CC. Out of the 8 SNHGs studied, 7 (SNHG5, SNHG12, SNHG14, SNHG16, SNHG17, SNHG20 and SNHG2/GAS5) can act as molecular sponges of miRNAs. **Conclusion**: Overall, this family of SNHGs is part of an interacting network, regulating important pathways for carcinogenesis. Thus, in the future, they may be used as biological markers and therapeutic targets in their wide applications in diagnosis and treatment. Further research is necessary to understand the role of SNHGs in cervical cancer.

Keywords: LncRNAs, cervical cancer, SNHG, metastasis, biomarker.

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LISTA DE SIGLAS E ABREVIATURAS

CC	Câncer Cervical
DNA	Ácido Desoxirribonucleico
EMT	Transição epitelial-mesenquimal
FIGO	Federação Internacional de Ginecologia e Obstetrícia
HPV	Papilomavírus Humano
HSIL	Lesão Intraepitelial escamosa de alto grau
INCA	Instituto Nacional de Câncer
LncRNAs	RNAs longos não codificantes
LSIL	Lesão Intraepitelial escamosa de baixo grau
miRNAs	MicroRNAs
ncRNAs	RNAs não codificantes
NIC	Neoplasias intraepiteliais cervicais
nt	Nucleotídeos
piRNA	RNA de interação com PIWI
rRNA	RNA Transportador
SNHGs	Small nucleolar host gene
snoRNA	Pequeno RNA nucleolar
snRNA	Pequeno RNA nuclear
TNM	Classification of Malignant Tumours
UFMA	Universidade Federal do Maranhão
UFPA	Universidade Federal do Pará

SUMÁRIO

1. INTRODUÇÃO

O Câncer Cervical (CC) é o quarto tipo de câncer feminino mais comum no mundo. Segundo dados publicados recentemente, estimou-se mundialmente o surgimento de 604.000 casos novos deste tipo de câncer para o ano de 2020 (SUNG et al., 2021). No Brasil, configura-se como o terceiro tipo de câncer mais incidente entre mulheres. São esperados para cada ano do triênio de 2023 a 2025, cerca de mais de 17 mil novos casos, correspondendo ao um risco estimado de 15,38 casos a cada 100 mil mulheres. Nas regiões Norte e Nordeste o CC é o segundo mais incidente, em relação à região Nordeste o estado do Maranhão possui uma alta taxa de incidência (21,71%) em relação aos demais estados e estima-se cerca de 800 novos casos de CC para o ano 2023 (INCA 2023).

O CC tem origem em um lento processo de ruptura da maturação normal da zona de transformação epitelial do cérvix uterino próximo a junção escamo colunar e é antecedido por lesões pré-cancerígenas conhecidas como neoplasias intraepiteliais cervicais (NIC) (BAVA SV et al., 2016). Sua etiologia está associada principalmente a infecção por HPV de alto risco (os tipos 16 e 18), reconhecidos como os principais causadores dessas neoplasias cervicais, que através da persistência viral podem levar ao desenvolvimento de lesões pré-cancerígenas, que são alterações nas células do colo do útero que não são cancerosas, mas têm o potencial de se tornarem cancerosas se não forem tratadas. (FONSECA et al., 2022; SCHIFFMAN et al., 2007; BHATLA et al., 2018).

Ressalta-se que nem todas as lesões do colo do útero progridem para câncer invasivo (DÍAZ-GONZÁLEZ et al., 2015), porém na ausência de sintomas específicos, a intima relação com a doença e o nível socioeconômico, muitos dos casos do CC são diagnosticados em estadiamento avançado devido na demora de busca pelo tratamento (THOUMI et al., 2021; SHERER et al., 2022). As opções de tratamento mais comuns para o CC incluem cirurgias, radioterapia, quimioterapias, imunoterapia e terapia alvo. As escolhas ou combinações desses tratamentos mais adequados vai variar de cada caso específico que deve ser feita pelo médico especialista (BHATLA N et al., 2021; SHERER et al., 2022; COHEN et al., 2019).

A ocorrência de metástases está amplamente associada a uma menor sobrevida nestas pacientes, pois uma vez ocorrida seus mecanismos de ação não estão totalmente esclarecidos para que possamos ter taxas de sobrevida melhores nesta população (ZHONG, YUE et al., 2020; GONG, Y et al., 2019). Diante disso, torna-se importante compreender mecanismos moleculares envolvidos no processo carcinogênese, um desses mecanismos envolvidos são os

RNAs longos não codificantes (LncRNAs), que detêm grande potencial em serem biomarcadores e portanto, podem revelar novas vias de sinalização auxiliando no prognóstico e tratamento mais adequado (HE, J et al., 2020; SHI, D et al., 2018; BHAN, A et al.,2017).

Os lncRNAs são moléculas endógenas de RNA de fita simples com mais de 200 nucleotídeos, não-codificantes de proteínas, os quais são capazes de participar de vários processos biológicos a níveis transcricional e pós-transcricional. Além disso, os lncRNAs possuem funcionalidade de interagir com outras moléculas reguladoras, incluindo proteínas e microRNAs, atuando como esponjas e afetando a expressão de seus alvos (CÁCERES-DURÁN et al., 2020; PENG WX et al., 2017). Estas biomoléculas ainda são pouco compreendidos e podem estar envolvidos em diversos processos biológicos, sendo associados aos processos de carcinogênese, progressão tumoral, metástase, proliferação celular, invasão, apoptose e o desenvolvimento de resistência a quimioterápicos (BHAN et al., 2017).

Dentre as classes de lncRNAs, podemos destacar os SNHGs, os quais tem sido extensivamente estudados em vários tipos de cânceres (NAJAFI et al., 2022; CHU et al., 2021). Um exemplo dos SNHGs temos o GAS5 que é expresso de forma anormal em várias malignidades humanas (YANG et al., 2020). O GAS5 é identificado como supressor tumoral, sendo regulado negativamente e participa de múltiplas funções biológicas, como proliferação celular, apoptose, migração, invasão e transição epitelial-mesenquimal (EMT) em câncer humano (YU et al., 2019; LIN et al., 2022). Em relação ao CC, este tipo de lncRNA ainda tem sido pouco explorada, mas alguns trabalhos apontam sobre o seu potencial papel como biomarcador. Desta forma, este trabalho tem como objetivo identificar os SNHGs relacionados com fatores de pior prognóstico no CC, através de uma busca sistemática da literatura.

2. REFERENCIAL TEÓRICO

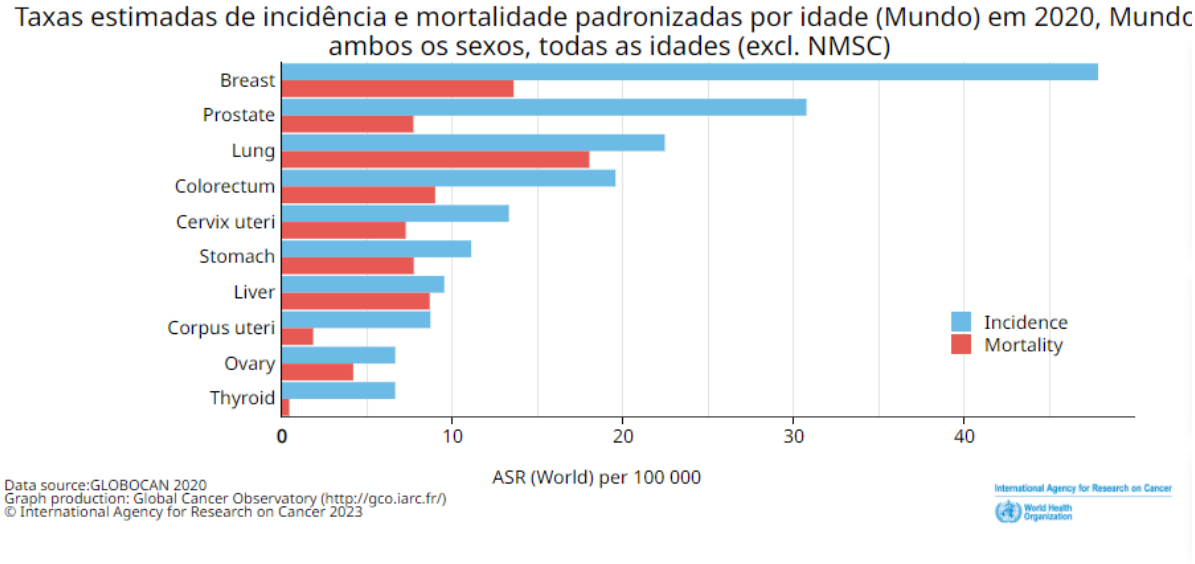
2.1 Câncer Cervical

Câncer é o nome geral dado a um conjunto de mais de 100 doenças, que têm em comum a divisão e crescimento desordenado de células cancerosas, determinando a formação de tumores que tendem a invadir tecidos e órgãos vizinhos (INCA, 2022).

O Câncer Cervical (CC) é a neoplasia mais comum em mulheres, excluindo tumores de pele não melanoma e mama, sendo a quarta causa de mortes por esta doença (7,3%) comparada a todos os outros tipos de cânceres femininos (GLOBOCAN, 2020). Em 2020, a estimativa de

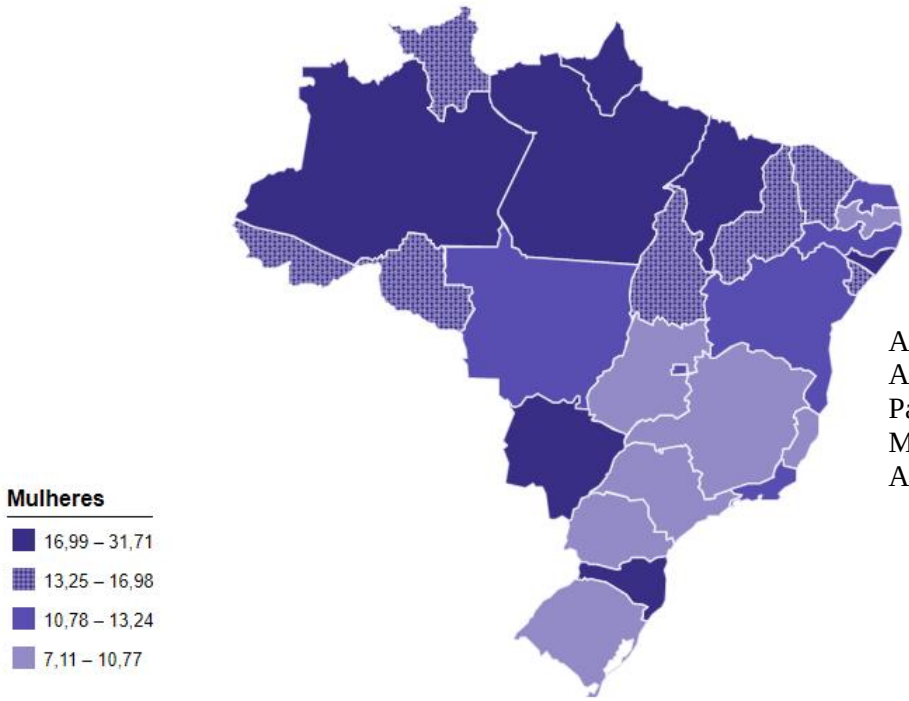
CC foi de mais 600.000 novos casos e 342.000 mortes em todo o mundo. Embora a incidência e a mortalidade relacionadas a esse câncer tenham diminuído nos últimos anos, devido à disponibilidade de programas de rastreamento, esta neoplasia maligna é configurada como os tipos de cânceres mais comumente diagnosticados em 23 países e é a principal causa de morte por câncer em 36 países. Com maiores taxas de incidência e mortalidade registradas em países africanos. A Figura 1 mostra os dados das estimativas de incidência e mortalidade por CC em 2020 (SUNG H et al., 2021; J FERLAY et al., 2020).

Figura 1. Estimativas de incidência e mortalidade por CC no mundo em 2020.



Dados divulgados pelo Instituto Nacional de Câncer, no Brasil o CC o terceiro câncer mais incidente em mulheres, para o triênio 2023/2025 estima-se 17.010 novos casos, representando um risco considerado de 13,25 casos para cada 100 mil mulheres. Configura-se como segundo mais incidente nas regiões Norte (20,48/100 mil) e Nordeste (21,71/100 mil). Na Região Centro-oeste (16,66/100 mil), ocupa a terceira posição; na Região Sul (14,55/100 mil), a quarta e na quinta posição a Região Sudeste com 12,93/100 mil mulheres. A Figura 2 apresenta o mapa de incidência de CC em cada estado do Brasil destacando os Estados com maiores indicies para 2023, esses dados estão expressos em 100 mil mulheres.

Figura 2. Incidência de câncer cervical no Brasil, para 2023.



Fonte: INCA 2022

O CC é caracterizado pela replicação desordenada do epitélio de revestimento do órgão, o que compromete o tecido subjacente (estroma) e pode invadir estruturas e órgãos próximos ou a distância. Essa doença possui duas categorias, tais como: carcinoma epidermóide, cerca de 90% dos casos, e o adenocarcinoma, câncer raro e que acomete o epitélio glandular (BRASIL, 2022).

O CC tem origem em um lento processo de ruptura da maturação normal da zona de transformação epitelial do cérvix uterino próximo a junção escamo colunar e é antecedido por lesões pré-cancerígenas conhecidas como neoplasias intraepiteliais cervicais (NIC) que são classificadas histologicamente com base nos aspectos morfológicos e progressivos das células epiteliais em: Lesão Intraepitelial escamosa de baixo grau (LSIL): NIC I/ displasia leve; Lesão intraepitelial escamosa de alto grau (HSIL): NIC II displasia moderada; NIC III displasia severa, carcinoma in situ, na qual pode evoluir para um câncer invasivo (ALRAJJAL A et al., 2021; BAVA SV et al., 2016). Sua etiologia está associada a infecção papilomavírus humano (HPV) de alto risco principalmente os tipos 16 e 18, reconhecidos como principais causadores das displasias cervicais, que através da persistência viral e consequente progressão das células infectadas para pré-câncer que futuramente podem promover para o câncer invasivo (SCHIFFMAN et al., 2007.; BHATLA et al., 2018).

Apesar de mais de 90% dos casos de CC serem causados por infecção persistente do HPV, este não é o suficiente para induzir a malignidade sendo necessários associações com outros cofatores de risco: início precoce da atividade sexual e múltiplos parceiros, tabagismo, a associação com Síndrome da Imunodeficiência Adquirida (Aids), uso prolongado de pílulas anticoncepcionais (GUL; MURAD; JAVED, 2015).

A maioria das lesões do colo do útero não progridem para um câncer invasivo, pois existe uma elevada chance de prevenção através da vacinação contra o HPV, facilidade de detectar precocemente as alterações através do exame citopatológico, viabilizando diagnóstico rápido e tratamento eficaz. Porém, nos estádios iniciais da doença a cura se justifica pela evolução lenta da doença, a mesma se manifesta de forma assintomática (chegando a durar cerca de 10 a 30 anos para o aparecimento das primeiras lesões), evoluindo para quadro avançado incluem hemorragia vaginal, dor pélvica, corrimento vaginal e dor durante o sexo, perda de peso, fadiga, dor abdominal acompanhadas por queixas urinárias, entre outros (DÍAZ-GONZÁLEZ, et al., 2015; MARTH C et al., 2017).

Quanto ao tratamento padrão para essa doença maligna pode ser composto por cirurgias, quimioterapia, radioterapia, imunoterapia e terapia alvo sendo que a escolha do tipo de intervenção dependerá do estadiamento da doença e fatores pessoais, como idade e desejo de ter filhos (HILL EK, 2020; COHEN et al., 2019). Infelizmente, a demora na busca de um diagnóstico precoce muitas mulheres apresentam doença em estágio metastático e o tratamento curativo não é mais alcançável, o que torna desafiador, pois a metástase estar associada a uma menor sobrevida da paciente e ainda não existem tratamentos eficazes para prevenir e inibi-la devido aos seus mecanismos de ação que ainda não estão totalmente esclarecidos (ZHONG, YUE et al., 2020; GONG, Y et al., 2019).

O CC é classificado de acordo com o Sistema TNM (Classification of Malignant Tumours), usado para classificar tumores malignos, com base na extensão anatômica da doença. Essa classificação leva em conta, a avaliação de três componentes: T – a extensão do tumor primário, N – a ausência ou presença e a extensão de metástase em linfonodos regionais e M – a ausência ou presença de metástase à distância. O estadiamento da FIGO (International Federation of Gynecology and Obstetrics) é baseado em informações clínicas, cirúrgicas e radiográficas, em todo o mundo é amplamente utilizada para ajudar a padronizar a classificação e a determinar a gravidade do CC, podendo direcionar qual o melhor tratamento para a paciente (SALEH et al., 2020; BHATLA et al., 2021). Seguindo as últimas alterações na classificação

da FIGO que foram implementadas em 2018 pelo seu comitê para oncologia ginecológica se classificam em quatro estádios de acordo coma Tabela 2 (BHATLA et al., 2018).

Tabela 1: Estadiamento da FIGO do câncer cervical (2018)

Estágio	Descrição
I	Carcinoma confinado ao colo do útero (deve-se desconsiderar a extensão em relação ao corpo uterino)
IA	Carcinoma diagnosticado apenas por microscopia, com invasão do estroma ≤ 5 mm de profundidade*
IA1	Invasão mensurada de estroma < 3 mm de profundidade
IA2	Invasão mensurada de estroma ≥ 3 mm e < 5 mm de profundidade
IB	Invasão medida ≥ 5 mm (maior que o estádio IA) com lesão limitada ao colo do útero.
IB1	Lesões < 2 cm na maior dimensão
IB2	Lesões ≥ 2 e 4 cm na maior dimensão
IB3	Lesões ≥ 4 cm na maior dimensão
II	Extensão além do útero, mas não até a parede pélvica ou até o terço inferior da vagina
IIA	Limitado a 2/3 superiores da vagina sem envolvimento parametrial óbvio
IIA1	Lesão ≤ 4 cm na maior dimensão
IIA2	Lesão > 4 cm na maior dimensão
IIB	Envolvimento parametrial, mas não até a parede pélvica
III	Extensão até a parede pélvica e/ou envolvimento do terço inferior da vagina, e/ou causa hidronefrose ou rim não funcional, e/ou envolve linfonodos pélvicos e/ou para-aórticos
IIIA	Extensão até o terço inferior da vagina, mas não até a parede pélvica
IIIB	Extensão até a parede pélvica e/ou causa hidronefrose ou rim não funcional (a menos que saiba que é devido a outra causa)
IIIC	Envolve os linfonodos pélvicos e/ou para-aórticos, independentemente do tamanho e extensão do tumor (com as notações r e p)
IIIC1	Apenas metástases nos linfonodos pélvicos
IIIC2	Metástases nos linfonodos para-aórticos
IV	Extensão para além da pelve verdadeira, ou envolvimento comprovado por biópsia da bexiga ou mucosa retal
IVA	Disseminação em órgãos pélvicos adjacentes

IVB	Disseminação para órgãos distantes

Fonte: Bhatla et al., 2018

Embora haja avanços na pesquisa molecular quanto ao CC, evidências contundentes indiquem que a infecção pelo HPV é uma pré-condição para a malignidade, ela não é suficiente para causar a carcinogênese cervical. Isso ocorre porque a carcinogênese também depende de variações genéticas individuais e modificações epigenéticas. Modificações epigenéticas, como metilação do DNA, modificação de histonas e RNAs não codificantes (ncRNAs), influenciam a expressão gênica sem alterações na sequência do DNA (HE J et al., 2020).

2.2 Longos RNAs não codificantes e câncer cervical

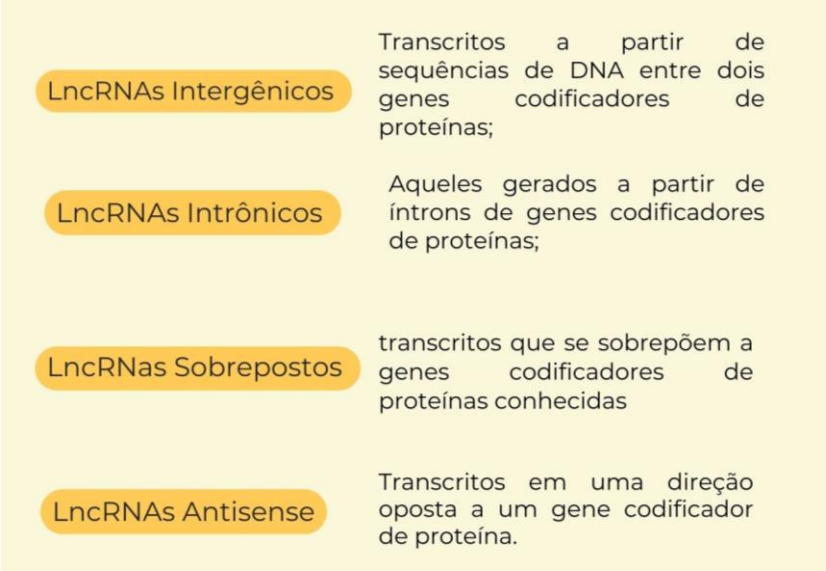
Os ncRNAs são geralmente divididos em duas categorias de acordo com seu tamanho: pequenos ncRNAs, transcritos que apresentam menos de 200 nucleotídeos (nt) de comprimento e longos ncRNAs (lncRNAs) maiores que 200 nt. Os pequenos ncRNAs incluem os bem caracterizados microRNAs (miRNAs), que atuam como importantes reguladores pós-transcricionais da expressão gênica via o complexo silenciador induzido por RNA (KWOK E TAY Y, 2017). Também entre os pequenos ncRNAs, podemos citar: RNA ribossômico (rRNA), RNA transportador (tRNA), pequeno RNA nuclear (snRNA), pequeno RNA nucleolar (snoRNA) e RNA de interação com PIWI (piRNA) (FERREIRA E ESTELLER, 2018).

Os lncRNAs são mais frequentemente transcritos pela RNA polimerase II, podem ter íntrons e variantes de splicing, podem exibir cauda poli A na extremidade 3 'e podem sofrer modificações epigenéticas semelhantes a genes que codificam proteínas, como regulação pela metilação do DNA e mudanças nas histonas (YAO et al., 2019). Existem muitos estudos na literatura quanto a função biológica dos lncRNAs, porém estes ainda são pouco compreendidos. Mas, estes podem estar envolvidos em diversos processos biológicos, sendo associados com os processos de carcinogênese, progressão tumoral, metástase, proliferação celular, invasão, apoptose e o desenvolvimento de resistência a quimioterápicos (APRILE M et al., 2020; SOGHLI N et al., 2020)

Os LncRNAs são capazes de participar de vários processos biológicos a níveis transcricional e pós-transcricional. Além disso, os lncRNAs possuem funcionalidade de interagir com outras moléculas reguladoras, incluindo proteínas e microRNAs, atuando como esponjas e afetando a expressão de seus alvos (CÁCERES-DURÁN ET AL., 2020; PENG, WX et al., 2017). Os lncRNas abrangem várias moléculas de RNA diferentes, por seu amplo espectro de funções, é difícil classificá-los, porém, sua classificação tradicional é baseada na

localização com relação a de genes codificantes próximos, permitindo a descrição em quatro categorias descritas na Figura 3 (BHAN A et al., 2017).

Figura 3- Categorias dos LncRNAs



Fonte: O autor.

Evidências de pesquisas anteriores indicam que a regulação positiva de lncRNAs promove o crescimento de células cancerígenas do colo do útero (SHEN et al., 2019; ZHANG & GAO 2017; ZHU et al., 2017; XU E ZHANG 2019; GUO et al., 2018; CHANG E SUN 2019; CHEN et al., 2019; HAN et al., 2018). Outros estudos mostraram que vários lncRNAs estão envolvidos na progressão do CC, incluindo H19, transcrição de adenocarcinoma pulmonar associado à metástase lncRNA 1 (MALAT1), RNA intergênico antisense HOX (HOTAIR), transcrição 1 associada ao câncer de cólon (CCAT1) e X- transcrição específica inativa (XIST) (OU et al., 2018; LIU et al., 2016; HAN et al., 2019; ZHENG et al., 2018; GUO et al., 2019; SHEN et al 2019; ZHANG & GAO 2017; ZHU et al., 2018).

2.3 SNHGs e Câncer Cervical

Os RNAs longos não codificantes denominados SNHGs (pequenos genes hospedeiros de RNA nucleolar) abrigam outros RNAs não codificantes, como os snoRNAs (pequenos RNAs nucleolares) (Qin Y et al., 2020). Este grupo de lncRNA participa na modulação da biologia do câncer de duas maneiras. A primeira seria como RNAs endógenos concorrentes (ceRNAs), os quais ocupam os sítios de ligação entre o microRNA (miRNA) e seus genes-alvo, impedindo

os efeitos inibitórios do miRNA no nível pós transcricional (YOON et al., 2014; LI et al., 2022). A segunda maneira os lncRNA SNHGs regulam certas vias de sinalização envolvidas na codificação de proteínas e influenciam a patogênese do tumor e a progressão no nível de expressão de proteínas (BIAGIONI et al., 2021).

Há evidências de que atualmente existem 22 membros da família SNHG (SNHG1 a SNHG22) e são expressos de forma anormal em múltiplos tipos de câncer, pois eles são considerados reguladores emergentes de uma ampla gama de processos biológicos como apoptose, invasão e migração (QIN et al., 2020; YANG et al., 2021). Os SNHGs, possui papel relevante na biologia tumoral, sugerindo que eles podem ser alvos terapêuticos em potencial para o tratamento do CC (ZIMTA AA et al., 2021). No entanto, são necessárias mais pesquisas para entender completamente o papel dos SNHGs no CC e seu potencial como alvos terapêuticos. É válido ressaltar, que na literatura ainda temos poucos estudos que elucidam a relação entre os lncRNAs-SNHGs e a carcinogênese do câncer cervical, tornando-se necessário uma ampla investigação destas moléculas. Portanto, esta revisão sistemática é importante para compreender o papel dos SNHGs na progressão do CC, afim de identificar novos alvos terapêuticos e orientar futuras pesquisas nesta área.

3. OBJETIVOS

Identificar SNHGs relacionados com fatores de pior prognóstico em câncer cervical, através de uma busca sistemática da literatura.

3.1. Objetivos Específicos:

- Selecionar na literatura LncRNAs da família SNHGs que encontram-se associados a fatores de pior prognóstico (FIGO, metástase linfonodal, grau histológico e tamanho do tumor) em câncer cervical.
- Apresentar a expressão desses LncRNAs selecionados na literatura se alta ou baixo comparado a amostra tumoral.
- Identificar os microRNAs alvos dos SNHGs observados.
- Destacar os genes alvos dos microRNAs regulados pelos LncRNAs.
- Evidenciar as vias de sinalização e os genes alvos.
- Identificar as funções biológicas dos SNHGs.

4. ARTIGO

TÍTULO: Papel dos SNHGS em fatores de pior prognóstico em Câncer Cervical: uma revisão sistemática.

Artigo enviado para a Revista Asian Pacific Journal of Cancer Prevention

Qualis A4

Role of SNHGs in factors of worse prognosis in Cervical Cancer: a systematic review

Running Title: SNHGs and Factors of Worse Prognostic in Cervical Cancer

Eleilde Almeida Araujo [1], Fernanda Jeniffer Lindoso Lima [1], Kaile de Araújo Cunha [1], Maria do Socorro de Sousa Cartagenes [1,2], Gyl Eanes Barros Silva [3], Jessica Manoelli Costa da Silva 4, André Salim Khayat 4, Fabiano Cordeiro Moreira [4], Juliana Maria Trindade Bezerra[5], Ana Gabriela Caldas Oliveira[6], Ana Gabrielly de Melo Matos[7], Jaqueline Diniz Pinho[8], Marcelo Souza de Andrade [1,2].

1) Federal University of Maranhão (UFMA), Graduate Program in Adult Health (PPGSAD), São Luís, Maranhão, Brazil.
2) Department of Physiological Sciences/CCBS, Federal University of Maranhão (UFMA), São Luís, Maranhão, Brazil.
3) Laboratory of Immunofluorescence and Electron Microscopy, University Hospital of the Federal University of Maranhão, São Luís, Brazil
4) Center for Research in Oncology, Federal University of Pará, Belém, Brazil.
5) Degree in Biological Sciences, Center for Higher Studies of Lago da Pedra, State University of Maranhão (CESLAP/UEMA), Lago da Pedra, Maranhão, Brazil.
6) Federal University of Maranhão, Department of Medicine III, Maranhão, Brazil.
7) State University of Maranhão (UEMA), Biological Sciences Bachelor, Bacabal, Maranhão, Brazil.
8) State University of Maranhão (UEMA), Department of Biological Sciences, Zé Doca, Maranhão, Brazil.

Corresponding Author

Jaqueline Diniz Pinho

Address: State University of Maranhão (UEMA), Department of Biological Sciences, Zé Doca, Maranhão, Brazil. *Email: jackdpinho@gmail.com*

Summary

Objective: Cervical Cancer (CC) is the fourth most common type of cancer in women around the world; in some regions of underdeveloped countries, however, it may even be the most frequent. Thus, it is important for us to understand the molecular elements involved in this process. Recently, a new class of long non-coding RNAs (LncRNAs), the host genes of small nucleolar RNA (SNHGs), has been frequently reported in various types of cancer in humans. Therefore, this study aims to summarize the main results described in the literature of the lncRNA family (SNHGs) in CC.

Methods: This study was conducted in conformation to the PRIMA-scR protocol, using the PICOS strategy. As research sources, we used the following databases: PubMed, ScienceDirect, Lilacs and Medline.

Results: Out of a total of 3,803 studies, we selected 12 which included 8 SNHGs (GAS5, SNHG5, SNHG7, SNHG12, SNHG14, SNHG16, SNHG17 and SNHG20) associated with CC; all, except for GAS5, presented an increased expression. In the literary survey carried out, the expression of SNHGs was associated with poor prognostic factors such as: proliferation, migration, invasion, metastasis and apoptosis in CC.

Conclusion: Although more studies are needed, these data demonstrate the important role of SNHGs in tumor biology and the promising role of this class of transcripts as a tool in the clinical management of CC.

Keywords: SNHG lncRNAs, cervical cancer, cell proliferation, metastasis.

Introduction

Cervical Cancer (CC) is the fourth most common type of cancer among women in the world (Sung et al., 2021). In Brazil, it is the third most incident type of cancer among women, and by 2023 more than 17,000 new cases of CC were estimated in the country. In some regions of Brazil, this malignant neoplasm is one of the main causes of female mortality by cancer. In the state of Maranhão, CC is the second most incident, with an estimated incidence of about 800 (21.13%) new cases (INCA 2023). Among its risk factors, Human Papillomavirus (HPV) infection stands out, especially subtypes 16 and 18 (Schiffman et al., 2007; Bhatla et al., 2018).

The occurrence of metastases is widely associated with a shorter survival in these patients. However, the mechanisms associated with the development of metastasis are not fully understood. Constriction of these carcinogenic pathways is essential to achieve better outcomes in the survival rates of these patients (Zhong, Yue et al., 2020; Gong, Y et al., 2019). Possible elements involved as potential biomarkers for prognosis and more appropriate treatment are long non-coding RNAs (lncRNAs) (He J et al., 2020; Shi D et al., 2018; Bhan A et al., 2017). LncRNAs are single-stranded endogenous RNA molecules with more than 200 nucleotides, non-protein coding, which are capable of participating in various biological processes at transcriptional and post-transcriptional levels. In addition, lncRNAs have the function of interacting with other regulatory molecules, including proteins and microRNAs, acting as sponges and affecting the expression of their targets (Cáceres-Durán et al., 2020; Peng Wx et al., 2017).

Some lncRNAs may harbor in their sequence other non-coding RNAs, such as nucleolar RNAs (snoRNAs), characterized as small molecules with average size ranging between 70-140 nucleotides in length (Zimta et al., 2020). Small nucleolar RNA host genes (SNHGs) are a group of lncRNAs that contain introns and exons in their sequences and generate, through alternative splicing, snoRNAs. To date, it has been reported that the SNHG family is composed of 22 members, from SNHG1 to SNHG22, which play significant roles related to proliferation, apoptosis, invasion, and migration (Biagioni A et al., 2021; Krishnan P et al., 2016).

The aberrant expression of the SNHGs family is a frequent alteration in several types of cancer, such as: thyroid (Qin Y et al., 2020; Ding W et al., 2020), breast (Ma Q et al., 2020; Xiong X et al., 2020), pancreas (Zhao L, et al., 2021; Shuwen Han et al., 2020), and prostate cancer (Wu G, et al., 2020; Zhang et al., 2017). In general, these studies demonstrate that this group of biomolecules may be a potential oncological biomarker. In relation to CC, studies are scarce and restricted to some SNHGs. Therefore, this systematic review aims to summarize the main aspects of this class of lncRNAs in CC.

Materials and Methods

Study Design and Protocol Registration

The present study is a systematic literature review that was registered in the International Prospective Register of Systematic Reviews (PROSPERO - https://www.crd.york.ac.uk/PROSPERO), under number CRD42022356239. We followed the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA - https://www.prisma-statement.org).

Study Question

This study is based on the following question: what is the association of SNHGs with poor prognostic factors in cervical cancer? For this purpose, we used the PRIMA-scR protocol, defining the PICOS anagram as: Population - patient with cervical cancer; intervention - efficacy of the biomarkers of the SNHG class; comparison - does not apply; outcome - relation to the expression of the biomarker; study design - only experimental studies.

Eligibility criteria

We included only: (1) articles in English, (2) published between the years 2017 to 2022 with (3) experimental studies that have as a casuistry patients who were diagnosed with cervical cancer and (4) that described the technique employed. The following were not included: (1) abstracts, reports, reviews, monographs, dissertations and (2) studies that use TCGA data as a casuistry.

Data Sources and Strategies

The searches were performed in the following electronic databases: U.S. National Library of Medicine (PubMed), ScienceDirect, Lilacs and Medline, in which the following descriptors were used: "LncRNAs and cervical cancer", "LncRNAs and uterine cancer", "LncRNAs and cervical cancer", SNHG1 cervical cancer, SNHG5 cervical cancer, SNHG6 cervical cancer, SNHG4 cervical cancer, SNHG7 cervical cancer, SNHG12 cervical cancer, SNHG16 cervical cancer and GAS5 cervical cancer.

Selection of Studies and Strategies

For data selection, duplicates and studies that did not meet the inclusion criteria were removed. We input information for each article on a Microsoft Excel 2019 datasheet. From each study, the following information was recorded: a) Clinicopathological characteristics: TNM, lymph node metastasis, stage, grade of cell differentiation and type of expression; b) Biological function of SNHGs: proliferation, migration, invasion, cell cycle, apoptosis, colony formation, participation in mesenchymal epithelium transition, and whether these lncRNAs target micro-RNAs and pathways; c) Clinical Indicators: diagnostic indicators, prognoses and biomarkers.

Evaluation of the methodological quality of the included studies

Researchers E. A. and A. G. evaluated the methodological quality of the 12 studies included, independently, using Joanna Institute Critical Appraisal Tools (JBI) (JBI, 2020). As represented in the table (Supplementary Table), each criterion was classified as "yes", "no", "unclear", "not applicable" individually for each article. The risk of bias classification was made according to these scores: a) 1 to 3 "yes", the risk of bias is high; b) 4 to 6 "yes", have moderate bias; c) 7 to 8 “yes”, low-risk bias.

Results

Literary Survey

Out of the 3,803 studies found in the four databases, 1,543 records were excluded after the removal of duplicates, and 2,082 articles removed post-screening of titles and abstracts. After further reading of the literature, 84 articles were reviews and 82 articles were excluded because they were articles that did not answer the study question, or were not published in English. After the inclusion criteria, a total of 12 studies remained. For more information on the process of article screening, see Figure 1.

From these 13 articles, our results demonstrate that the vast majority of SNHGs are overexpressed, acting as fundamental regulators of processes such as: invasion, cell proliferation, apoptosis, cell cycle, mesenchymal epithelial transition, colony formation and migration. In Table 1 we observe the information related to the techniques used, as well as the characteristics of the biological samples, clinical and histopathologic parameters in the CC. Additional information is summarized in Table 1.

Of the 8 SNHGs studied, after analyzing the type of expression, target gene and signaling pathways, Table 2 shows 7 SNHGs studied (SNHG5, SNHG12, SNHG14, SNHG16, SNHG17, SNHG20 and SNHG2/GAS5) that can act as sponge molecules of miRNAs, thus participating in a variety of important biological processes, such as cell proliferation, apoptosis, migration and invasion (Chu et al., 2021).

Discussion

GAS5

The specific transcript 5 for growth arrest (GAS5) also known as SNHG2, is a tumor suppressor and is located on chromosome 1q25, with ~630 nucleotides (Ma C et al, 2016). According to the study by Y. **Li et al**., **(2018)** decreased expression of GAS5 was associated with parameters for poor prognosis FIGOIIa lymph node metastasis, in addition to facilitating and increasing cell invasion, migration. In another study, Fang et al. (2020) observed that GAS5 is transcriptionally modulated by p-STAT3, in addition to acting as a miR-21 ceRNA, which in turn is capable of regulating PDCD4. MiR-21 is an oncogenic microRNA that has been touted as key in the development and progression of cervical malignancy (Gebrie A, 2022). Although GAS5 has been little explored in cervical cancer, so far, the data demonstrate that this lncRNA has the potential to be a biomarker in this type of neoplasm.

SNHG5

The host gene of small nucleolar RNA 5 (SNHG5) located on chromosome 6q14.3, is involved in the development and tumorigenesis of a variety of cancers, such as: colorectal, bladder, gastric and endometrial cancer (Li, Y et al., 2020). Studies of the association of SNGH5 with CC are still rare, but the data from this study revealed its overexpression associated with the FIGO II stage and with the presence of lymph node metastasis. This overexpression promotes the expression of SOX4, while that of miR-132 is decreased; with the silencing of SNHG5 there was an increase in proliferation, migration and invasion through the downregulation of miR-132 (Zhang, L et al., 2021).

SNHG7

The host gene of small nucleolar RNA 7 (SNHG7) located on chromosome 9q34.3 is one of the oncogenic lncRNAs that has had its mechanism of action investigated in several human cancers, such as cervical cancer (Chi et al., 2020; Najafi S et al., 2022). Suppression of SNHG7 was observed in CC tissues associated with factors of worse survival, in addition to regulating factors involved with the mesenchymal epithelial transition (TMS), such as N-cadherin and Vimentin (Zeng et al., 2019). TMS is a process implicated in cancer progression and metastasis, whereby epithelial cancer cells lose cell polarity and cell-to-cell adhesions and gain metastatic and invasive properties (Ribatti et al., 2020).

SNHG12

The lncRNA small nucleolar RNA host gene 12 (SNHG12) is located on chromosome 1p35.3 and has already been described in the literature as a new oncogene for cancer. Its expression may be related to poor prognosis and accelerates tumorigenesis (Chen, et al., 2020). The biological role of SNHG12 in CC is still poorly comprehended, but it has been demonstrated that SNHG12 expression was significantly increased in CC tissues compared to normal tissues. In addition, this survey found that the expression of SNHG12 was significantly higher in FIGO stage II, that is, when the carcinoma invades beyond the uterus, but does not extend to the lower third of the vagina or the pelvic wall. It was possible to observe that the overexpression of SNHG12 can promote cell proliferation and migration, but more investigations are still needed regarding its mechanisms of action (Dong, et al., 2018).

SNHG14

The host gene 14 of the small nucleolar RNA of long non-coding RNA (SNHG14), also known as UBE3A-ATS, acts as a key regulator of cellular processes in several types of human cancers (Zhang H et al., 2020). There are two articles that relate SNHG14 to CC. In the first study, Zhang et al., (2019) reported a high expression of SNHG14 in poor prognostic factors, with emphasis on the presence of metastasis. The second study, in addition to corroborating these findings, also described that they found that SNHG14 overexpression has the potential to promote cell proliferation, migration, and invasion, suggesting an important role as a therapeutic target for CC via the miR-206/YWHAZ axis (Ji N et al., 2019).

SNHG16

The biological roles of the small nucleolar RNA host gene 16 (SNHG16) have recently been investigated in the progression of several types of cancers, especially because this lncRNA has a role as an endogenous competitor (Xu, et al., 2018; Yang., et al 2019).

In CC, Tao et al. (2020) evidenced that SNHG16 is able to promote tumor invasion, through the recruitment of transcription factors such as RLS1, to regulate the expression of PARP9. Wu et al. (2020) suggested that SNHG16 may serve as an oncogene capable of promoting tumor progression by acting as miR-216a-5p/ZEB1 ceRNA. The ZEB1 gene acts directly in promoting TMS, as well as correlating with poor staging in cancer patients (Zhang et al., 2015). In another study, using expression inhibition assays, SNHG16 was also observed associated with EMT, in addition to increasing miR-128 expression and inactivating the WNT/β-catenin pathway. In this same work, the authors associated the aberrant expression of SNHG16 to the stage and size of the tumor (Zhu et al., 2018). The WNT/β-catenin signaling pathway has been widely studied in cancer due to its potential to present therapeutic targets (Nusse et al., 2017).

SNHG17

The host gene of small nucleolar RNA 17 (SNHG17) located at 20q11 has been reported to be overexpressed in ovarian cancer (Zheng ZJ et al., 2020), as well as colorectal cancer (Bian Z et al., 2021), promoting proliferation and tumorigenesis. However, the biological and regulatory function of SNHG17 in CC is still unclear, since to date there are rare studies such as the one by Cao S et al., 2021, reporting that this lncRNA was overexpressed in serum samples from patients with CC. It was also found that SNHG17 expression was significantly higher in FIGO II stage II (when a carcinoma expands its extension beyond the uterus, but not to the

pelvic wall) and in lymph node metastasis. Their results also showed that miR-375-3p can be a direct target of SNHG17, since the knockdown of SNHG17 was able to inhibit cell growth through the repression of miR-375-3p expression, which may act as a prospective diagnostic marker and potential therapeutic targets for CC, requiring further research.

SNHG20

The small nucleolar RNA host gene 20 (SNHG20) is located at 17q25.2, and plays an important role in CC in terms of prognosis and tumor progression, invasion, metastasis, and apoptosis (Aalijahan and Ghorbian, 2019). As for the expression of this lncRNA, Guo et al. (2018) evidenced that the expression of SNHG20 was significantly increased in CC, in tumors of larger size, advanced stage of FIGO and lymph node metastasis l. As for its biological role, they observed through interference assays that SNHG20 regulates miR-140-5p; this, in turn, targets ADAM10 and reduces the phosphorylation of MEK1/2, ERK1/2 and p38.

Conclusion

There is a growing number of studies showing deregulated lncRNAs in the carcinogenic process, as they are potential oncogenes or tumor suppressors that play important roles in cervical cancer. The family of SNHGs described in this research may, in the future, be used as biological markers and therapeutic targets in their wide applications in the diagnosis and treatment of cervical cancer. We emphasize the importance of conducting more studies regarding their biological role and clinical application.

Authors' contributions
All authors contributed to the construction of this article with suggestions, writing of segments, survey in databases and/or data analysis.

Conflict of Interest:
The authors declare that there is no conflict of interest.

References

1. Aalijahan H, Ghorbian S. Long non-coding RNAs and cervical cancer. Exp Mol Pathol. 2019; **106**:7-16.
2. Amant F, Mirza Mr, Creutzberg Cl. Cancer of the corpus uteri. Int J Gynaecol Obstet; 2015; **119**:110-7.

3. Bhan A, Soleimani M, Mandal SS. Long Noncoding RNA and Cancer: A New Paradigm. Cancer Res. 2017; **77**(15):3965-3981.
4. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. Int J Gynaecol Obstet. 2018; **143** Suppl 2:22-36.
5. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri: 2021 update. Int J Gynaecol Obstet. 2021;**28**-44.
6. Biagioni A, Tavakol S, Ahmadirad N, Zahmatkeshan M, Magnelli L, Mandegary A, Samareh Fekri H, Asadi MH, Mohammadinejad R, Ahn KS. Small nucleolar RNA host genes promoting epithelial-mesenchymal transition lead cancer progression and metastasis. IUBMB Life. 2021; **73**(6):825-842.
7. Bian Z, Zhou M, Cui K, Yang F, Cao Y, et al. SNHG17 promotes colorectal tumorigenesis and metastasis via regulating Trim23-PES1 axis and miR-339-5p-FOSL2-SNHG17 positive feedback loop. J Exp Clin Cancer Res. 2021;**40**(1):360.
8. Cáceres-Durán MÁ, Ribeiro-Dos-Santos Â, Vidal AF. Roles and Mechanisms of the Long Noncoding RNAs in Cervical Cancer. Int J Mol Sci. 2020; **21**(24):9742.
9. Cao S, Li H, Li L. LncRNA SNHG17 Contributes to the Progression of Cervical Cancer by Targeting microRNA-375-3p. Cancer Manag Res. 2021;**13**:4969-4978.
10. Cao S, Liu W, Li F, Zhao W, Qin C. Decreased expression of lncRNA GAS5 predicts a poor prognosis in cervical cancer. Int J Clin Exp Pathol. 2014;**7**(10):6776-83.
11. Chen L, Zhang X, Han B, Dai H. Long Noncoding RNA SNHG12 Indicates the Prognosis and Accelerates Tumorigenesis of Diffuse Large B-Cell Lymphoma Through Sponging microR-195. OncoTargets and therapy. 2020; **13**: 5563–5574.
12. Chu Q, Gu X, Zheng Q, Guo Z, Shan D, Wang J, Zhu H. Long noncoding RNA SNHG4: a novel target in human diseases. Cancer Cell Int. 2021; **21**(1):583
13. Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. Lancet. 2019;**393**(10167):169-182.
14. Díaz-González Sdel M, Deas J, Benítez-Boijseauneau O, Gómez-Cerón C, Bermúdez-Morales VH, et al. Utility of microRNAs and siRNAs in cervical carcinogenesis. Biomed Res Int. 2015; **2015**:374924.
15. Ding W, Zhao S, Shi Y, Chen S. Positive feedback loop SP1/SNHG1/miR-199a-5p promotes the malignant properties of thyroid cancer. Biochem Biophys Res Commun. 2020; **522**(3):724-730.

16. Dong J, Wang Q, Li L, Xiao-Jin Z. Upregulation of Long Non-Coding RNA Small Nucleolar RNA Host Gene 12 Contributes to Cell Growth and Invasion in Cervical Cancer by Acting as a Sponge for MiR-424-5p. Cell Physiol Biochem. 2018; **45**(5):2086-2094
17. Fang X, Zhong G, Wang Y, Lin Z, Lin R, Yao T. Low GAS5 expression may predict poor survival and cisplatin resistance in cervical cancer. Cell Death Dis. 2020; **11**(7):531.
18. Gao J, Liu L, Li G, Cai M, Tan C, Han X, Han L. LncRNA GAS5 confers the radio sensitivity of cervical cancer cells via regulating miR-106b/IER3 axis. Int J Biol Macromol. 2019; **126**:994-1001.
19. Gebrie A. Disease progression role as well as the diagnostic and prognostic value of microRNA-21 in patients with cervical cancer: A systematic review and meta-analysis. PLoS One. 2022 Jul 27;**17**:e0268480.
20. Gong Y, Wan JH, Zou W, Lian GY, Qin JL, Wang QM. MiR-29a inhibits invasion and metastasis of cervical cancer via modulating methylation of tumor suppressor SOCS1. Future Oncol. 2019; **15**:1729-1744.
21. Guo H, Yang S, Li S, Yan M, Li L, Zhang H. LncRNA SNHG20 promotes cell proliferation and invasion via miR-140-5p-ADAM10 axis in cervical cancer. Biomed Pharmacother. 2018; **102**:749-757.
22. He J, Huang B, Zhang K, Liu M, Xu T. Long non-coding RNA in cervical cancer: From biology to therapeutic opportunity. Biomed Pharmacother. 2020; **127**:110209.
23. Instituto Nacional De Câncer José Alencar Gomes Da Silva. Estimativa 2023: incidência de câncer no Brasil / Instituto Nacional de Câncer José Alencar Gomes da Silva. – Rio de Janeiro : INCA, 2023.
24. Ji N, Wang Y, Bao G, Yan J, Ji S. LncRNA SNHG14 promotes the progression of cervical cancer by regulating miR-206/YWHAZ. Pathol Res Pract. 2019; **215** (4):668-675.
25. Ji YY, Meng M, Miao Y. lncRNA SNHG1 Promotes Progression of Cervical Cancer Through miR-195/NEK2 Axis. Cancer Manag Res. 2020; **12**:11423-11433
26. Krishnan P, Ghosh S, Wang B, Heyns M, Graham K, Mackey JR, et al. Profiling of Small Nucleolar Rnas by Next Generation Sequencing: Potential New Players for Breast Cancer Prognosis. PloS One. 2016; **11**(9):0162622.

27. Lai SY, Guan HM, Liu J, Huang LJ, Hu XL, Chen YH, Wu YH, Wang Y, Yang Q, Zhou JY. Long noncoding RNA SNHG12 modulated by human papillomavirus 16 E6/E7 promotes cervical cancer progression via ERK/Slug pathway. J Cell Physiol. 2020;**235**(11):7911-7922
28. Li H, Hong J, Wijayakulathilaka WSMA. Long non-coding RNA SNHG4 promotes cervical cancer progression through regulating c-Met via targeting miR-148a-3p. Cell Cycle. 2019;**18**(23):3313-3324
29. Li H, Hong J, Wijayakulathilaka WSMA. Long non-coding RNA SNHG4 promotes cervical cancer progression through regulating c-Met via targeting miR-148a-3p. Cell Cycle. 2019;**18**(23):3313-3324.
30. Li Y, Wan YP, Bai Y. Correlation between long strand non-coding RNA GASS expression and prognosis of cervical cancer patients. Eur Rev Med Pharmacol Sci. 2018;**22**(4):943-949
31. Najafi S, Ghafouri-Fard S, Hussen BM, Jamal HH, Taheri M, Hallajnejad M. Oncogenic Roles of Small Nucleolar RNA Host Gene 7 (SNHG7) Long Noncoding RNA in Human Cancers and Potentials. Front Cell Dev Biol. 2022; **9**:809345.
32. Nusse R, Clevers H. Wnt/β-Catenin Signaling, Disease, and Emerging Therapeutic Modalities. Cell. 2017 Jun 1;**169**:985-999.
33. Peng WX, Koirala P, Mo YY. LncRNA-mediated regulation of cell signaling in cancer. Oncogene. 2017;**36**(41):5661-5667.
34. Qin Y, Sun W, Wang Z, Dong W, He L, Zhang T, Zhang H. Long Non-Coding Small Nucleolar RNA Host Genes (SNHGs) in Endocrine-Related Cancers. Onco Targets Ther. 2020; **13**:7699-7717.
35. Ribatti D, Tamma R, Annese T. Epithelial-Mesenchymal Transition in Cancer: A Historical Overview. Transl Oncol. 2020 Jun;**13**(6):100773
36. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet. 2007; **370** :890-907.
37. Shen H, Mo Q, Xu X, Liu B. The prognostic value of lncRNA SNHG6 in cancer patients. Cancer Cell Int. 2020**; 20**:286
38. Shen Y, Liu S, Fan J, Jin Y, Tian B, Zheng X, Fu H. Nuclear retention of the lncRNA SNHG1 by doxorubicin attenuates hnRNPC-p53 protein interactions. EMBO Rep. 2017; **18**(4):536-548.

39. Shi D, Zhang C, Liu X. Long noncoding RNAs in cervical cancer. J Cancer Res Ther. 2018;**14**(4):745-753.
40. Shuwen Han, Yangyang Xie, Xi Yang et al. Small Nucleolar RNA and Small Nucleolar RNA Host Gene Signatures as Biomarkers for Pancreatic Cancer. Preprint. 2020;**1**.
41. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021; **71**:209-249.
42. Tang Y, Wu L, Zhao M, Zhao G, Mao S, Wang L, Liu S, Wang X. LncRNA SNHG4 promotes the proliferation, migration, invasiveness, and epithelial-mesenchymal transition of lung cancer cells by regulating miR-98-5p. Biochem Cell Biol. 2019; **97**(6):767-776.
43. Tao L, Wang X, Zhou Q. Long noncoding RNA SNHG16 promotes the tumorigenicity of cervical cancer cells by recruiting transcriptional factor SPI1 to upregulate PARP9. Cell Biol Int. 2020; **44**(3):773-784.
44. Tian X, Liu Y, Wang Z, Wu S. lncRNA SNHG8 promotes aggressive behaviors of nasopharyngeal carcinoma via regulating miR-656-3p/SATB1 axis. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2020; **131**: 110564.
45. Wen Q, Liu Y, Lyu H, et al. Long Noncoding RNA GAS5, Which Acts as a Tumor Suppressor via microRNA 21, Regulates Cisplatin Resistance Expression in Cervical Cancer. Int J Gynecol Cancer. 2017;**27**(6):1096-1108
46. Wu W, Guo L, Liang Z, Liu Y, Yao Z. Lnc-SNHG16/miR-128 axis modulates malignant phenotype through WNT/β-catenin pathway in cervical cancer cells. J Cancer. 2020; **11**(8):2201-2212
47. Wu, G, Hao, C., Qi, X. et al. LncRNA SNHG17 aggravated prostate cancer progression through regulating its homolog SNORA71B via a positive feedback loop. Cell Death Dis. 2020; **11**, 393.
48. Xiong X, Feng Y, Li L, Yao J, Zhou M, Zhao P, Huang F, Zeng L, Yuan L. Long non-coding RNA SNHG1 promotes breast cancer progression by regulation of LMO4. Oncol Rep. 2020; **43**(5):1503-1515.
49. Xu F, Zha G, Wu Y, Cai W, Ao J. Overexpressing lncRNA SNHG16 inhibited HCC proliferation and chemoresistance by functionally sponging hsa-miR-93. Onco Targets Ther. 2018; **11**:8855-8863.

50. Xu X, Xie Q, Xie M, Zeng Y, Liu Q. LncRNA SNHG8 Serves as an Oncogene in Breast Cancer Through miR-634/ZBTB20 Axis. Cancer management and research. 2021; **13**:3017–3028.
51. Yan Z, Ruoyu L, Xing L, Hua L, Jun Z, Yaqin P, Lu W, Aili T, Yuzi Z, Lin M, Huiping T. Long non-coding RNA GAS5 regulates the growth and metastasis of human cervical cancer cells via induction of apoptosis and cell cycle arrest. Arch Biochem Biophys. 2020; **684**:108320.
52. Yang M, Wei W. SNHG16: A Novel Long-Non Coding RNA in Human Cancers. Onco Targets Ther. 2019 **12**:11679-11690.
53. Yang W, Hong L, Xu X, Wang Q, Huang J, Jiang L. LncRNA GAS5 suppresses the tumorigenesis of cervical cancer by downregulating miR-196a and miR-205. Tumour Biol. 2017;**39(**7): 1010428317711315.
54. Yang W, Xu X, Hong L, Wang Q, Huang J, Jiang L. Upregulation of lncRNA GAS5 inhibits the growth and metastasis of cervical cancer cells. J Cell Physiol. 2019; **234**(12):23571-23580.
55. Yang W, Xu X, Hong L, Wang Q, Huang J, Jiang L. Upregulation of lncRNA GAS5 inhibits the growth and metastasis of cervical cancer cells. J Cell Physiol. 2019; **234**(12):23571-23580.
56. Yao T, Lu R, Zhang J, Fang X, Fan L, Huang C, Lin R, Lin Z. Growth arrest-specific 5 attenuates cisplatin-induced apoptosis in cervical cancer by regulating STAT3 signaling via miR-21. J Cell Physiol. 2019;**234**(6):9605-9615.
57. Zeng J, Ma YX, Liu ZH, Zeng YL. LncRNA SNHG7 contributes to cell proliferation, invasion and prognosis of cervical cancer. Eur Rev Med Pharmacol Sci. 2019;**23**(21):9277-9285.
58. Zeng J, Ma YX, Liu ZH, Zeng YL. LncRNA SNHG7 contributes to cell proliferation, invasion and prognosis of cervical cancer. Eur Rev Med Pharmacol Sci. 2019;**23**(21):9277-9285
59. Zhang H, Xu HB, Kurban E, Luo HW. LncRNA SNHG14 promotes hepatocellular carcinoma progression via H3K27 acetylation activated PABPC1 by PTEN signaling. Cell Death Dis. 2020; **11**(8):646.
60. Zhang J, Liu B, Zhang P, Wang L, Zhu Y. Knockdown of SNHG1 inhibits cervical cancer growth through sponging miR-194 to regulate HCCR. Gynecol Endocrinol. 2020; **36**(11):1028-1034

61. Zhang L, Wu X, Li Y, Teng X, Zou L, Yu B. LncRNA SNHG5 promotes cervical cancer progression by regulating the miR-132/SOX4 pathway. Autoimmunity. 2021;**54**(2):88-96.
62. Zhang L, Wu X, Li Y, Teng X, Zou L, Yu B. LncRNA SNHG5 promotes cervical cancer progression by regulating the miR-132/SOX4 pathway. Autoimmunity. 2021;**54**(2):88-96.
63. Zhang M, Wang W, Li T, Yu X, Zhu Y, Ding F, Li D, Yang T. Long noncoding RNA SNHG1 predicts a poor prognosis and promotes hepatocellular carcinoma tumorigenesis. Biomed Pharmacother. 2016; **80**:73-79.
64. Zhang P, Li S, Chen Z, Lu Y, Zhang H. LncRNA SNHG8 promotes proliferation and invasion of gastric cancer cells by targeting the miR-491/PDGFRA axis. Hum Cell. 2020 ;**33**(1):123-130
65. Zhang P, Sun Y, Ma L. ZEB1: at the crossroads of epithelial-mesenchymal transition, metastasis and therapy resistance. Cell Cycle. 2015;**14**(4):481-7.
66. Zhang Y, Su X, Kong Z, Fu F, Zhang P, Wang D, Wu H, Wan X, Li Y. An androgen reduced transcript of LncRNA GAS5 promoted prostate cancer proliferation. PLoS One. 2017 **12**(8):0182305
67. Zhang YY, Li M, Xu YD, Shang J. LncRNA SNHG14 promotes the development of cervical cancer and predicts poor prognosis. Eur Rev Med Pharmacol Sci. 2019; **23**(9):3664-3671.
68. Zhao L, Ye J, Lu Y, Sun C, Deng X. lncRNA SNHG17 promotes pancreatic carcinoma progression via cross-talking with miR-942. Am J Transl Res. 2021; **13**(3):1037-1050.
69. Zheng ZJ, Liu Y, Wang HJ, Pang WW, Wang Y. LncRNA SNHG17 promotes proliferation and invasion of ovarian cancer cells through up-regulating FOXA1. Eur Rev Med Pharmacol Sci. 2020; **24(**18):9282-9289.
70. Zhong Y, Lu Q, Qiu W, Luo Y. LINC00636 promotes lymph node metastasis and cervical cancer through targeting NM23. Biosci Rep. 2020; **40**(10).
71. Zhu H, Zeng Y, Zhou CC, Ye W. SNHG16/miR-216-5p/ZEB1 signal pathway contributes to the tumorigenesis of cervical cancer cells. Arch Biochem Biophys. 2018; **637**:1-8.
72. Zimta AA, Tigu AB, Braicu C, Stefan C, Ionescu C, Berindan-Neagoe I. An Emerging Class of Long Non-coding RNA With Oncogenic Role Arises From the snoRNA Host Genes. Front Oncol. 2020; **7**:10-89

Figure 1. Fluxogram of the study screening.

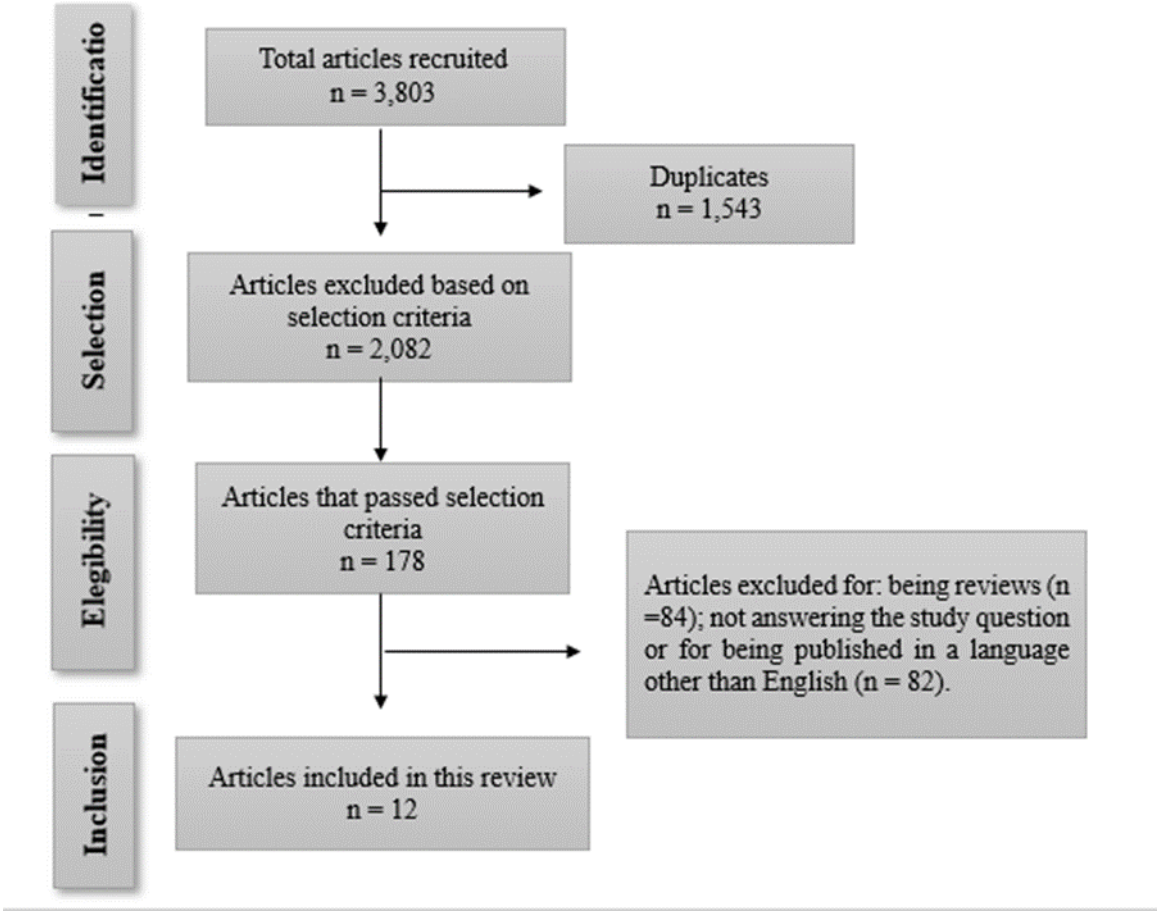


Table 1. Functional characterization and clinical significance of lncRNAs in cervical cancer.

LncRNA	Expression level	Samples	Tecniques	Biological role	Clinical significance	Reference
SNHG5	Overexpressed	tumor tissue and cell lineage	qRT-PCR	proliferation, migration and invasion	FIGO II and lymph node metastasis	Zhang L., et al., 2021
SNHG7	Overexpressed	tumor tissue and cell lineage	qRT-PCR	proliferation, migration and EMT	TNM III-IV, lymph node metastasis	J Zeng et al., 2019
SNHG12	Overexpressed	tumor tissue and cell lineage	qRT-PCR	proliferation, migration and invasion	FIGO II, lymph node metastasis	Dong J et al, 2018
SNHG14	Overexpressed	tumor tissue and cell lineage	qRT-PCR	proliferation, promotion of apoptosis	FIGO III-IV, tumor size ≥ 4 cm	Zhang YY et al., 2019
	Overexpressed	tumor tissue and cell lineage	qRT-PCR	cell proliferation, migration and invasion and promotion of apoptosis	FIGO III-IV, lymph node metastasis	Ji N et al., 2019
SNHG16	Overexpressed	tumor tissue and cell lineage	qRT-PCR	proliferation, migration and EMT	FIGO IIb-III, lymph node metastasis, poorly differentiated tumor and tumor diameter	Zhu H, et al., 2018
	Overexpressed	tumor tissue and cell lineage	qRT-PCR	proliferation, migration	TNM IIIa, tumor size, worse survival and poorly differentiated tumor	Tao L et al., 2020
	Overexpressed	tumor tissue and cell lineage	qRT-PCR	proliferation, EMT, migration and invasion	TNM III-IV, tumor size ≥ 5 cm,	Wu W et al., 2020
SNHG17	Overexpressed	blood samples	qRT-PCR	proliferation, migration and invasion	FIGO III-IV, lymph node metastasis, tumor diameter	Cao S et al., 2021

SNHG20	Overexpressed	tumor tissue and cell lineage	qRT-PCR	Proliferation, migration	FIGO IIb-IIa, lymph node metastasis, tumor size	Guo H et al., 2020
GAS5	Decreased	tumor tissue and cell lineage	qRT-PCR	proliferation, invasion	FIGO IIa, lymph node metastasis	Y. LI et al., 2018
	Decreased	tumor tissue and cell lineage	qRT-PCR	promotion of apoptosis	FIGO III-IV, lymph node metastasis	Fang X et al., 2020

Table 2. LncRNAs and microRNAs associated with cervical cancer.

LncRNA	MicroRNAs	Expression	Target Gene	Signaling pathways	References
SNHG5	miR-132	down-regulated.	SOX4	-	Zhang L et al., 2021
SNHG12	miR-424-5p	down-regulated.	-	-	Dong J et al, 2018
SNHG14	miR-206	down-regulated.	YWHAZ	-	Ji N et al., 2019
SNHG16	miR-216-5p	down-regulated.	ZEB1	-	Zhu H et al., 2018
	miR-128	down-regulated.	GSPT1 and WNT3A	WNT/β-catenin	Wu W et al., 2020
SNHG17	miR-375-3p	down-regulated.	-	-	Cao S et al., 2021
SNHG20	miR140-5p	down-regulated.	ADAM10	MEK/ERK	Guo H et al., 2018
GAS5	miR-21	down-regulated.	PDCD4	-	Fang X et al., 2020

Supplementary Table on the quality assessment of the studies

References	Quality Evaluation										
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total (YES)	Level of Bias
Zhang L et al., 2021	YES	YES	NO	YES	U	YES	YES	YES	YES	7	low-risk
Zeng J et al., 2019	YES	YES	NA	YES	NO	YES	NO	YES	YES	6	moderate
Dong J et al., 2018	YES	YES	U	YES	NA	YES	YES	YES	YES	7	moderate
Zhang YY et al., 2019	YES	YES	U	YES	NO	YES	YES	YES	YES	7	low-risk
Ji N et al., 2019	YES	YES	NA	YES	U	YES	NA	YES	YES	6	moderate
Zhu H et al., 2018	YES	YES	NA	YES	NO	YES	NA	YES	YES	6	moderate
Tao L et al., 2020	YES	YES	NO	YES	NA	YES	YES	YES	YES	7	low-risk
Wu W et al., 2020	YES	YES	U	YES	NO	YES	NA	YES	YES	6	moderate
Cao S et al., 2021	YES	YES	U	YES	U	YES	YES	YES	YES	7	low-risk
Guo H et al., 2020	YES	YES	U	YES	NA	YES	YES	YES	YES	7	low-risk
Li Y et al., 2018	YES	YES	NO	YES	NO	YES	NO	YES	YES	6	moderate
Fang X et al., 2020	YES	YES	U	YES	NO	YES	YES	YES	YES	7	low-risk

Yes; No; Unclear (U); Not applicable (NA)

REFERÊNCIAS

ALRAJJAL A, PANSARE V, CHOUDHURY MSR, KHAN MYA, SHIDHAM VB. Squamous intraepithelial lesions (SIL: LSIL, HSIL, ASCUS, ASC-H, LSIL-H) of Uterine Cervix and Bethesda System. Cytojournal. 2021; 17;18:16. doi: 10.25259/Cytojournal_24_2021.

BAVA SV, THULASIDASAN AK, SREEKANTH CN, ANTO RJ. Cervical cancer: A comprehensive approach towards extermination. Ann Med. (2016);48(3):149-161.

BHAN A, SOLEIMANI M, MANDAL SS. Long Noncoding RNA and Cancer: A New Paradigm. Cancer Res. 2017; 77(15):3965-3981.

BHAN A, SOLEIMANI M, MANDAL SS. Long Noncoding RNA and Cancer: A New Paradigm. Cancer Res. 2017; 77(15):3965-3981

BHATLA N, AOKI D, SHARMA DN, SANKARANARAYANAN R. Cancer of the cervix uteri. Int J Gynaecol Obstet. 2018;143(Suppl 2):22–36

BHATLA N, SINGHAL S, DHAMIJA E, MATHUR S, NATARAJAN J, MAHESHWARI A. Implications of the revised cervical cancer FIGO staging system. Indian J Med Res. 2021 Aug;154(2):273-283.

BIAGIONI A, TAVAKOL S, AHMADIRAD N, ZAHMATKESHAN M, MAGNELLI L, MANDEGARY A, SAMAREH FEKRI H, ASADI MH, MOHAMMADINEJAD R, AHN KS. Small nucleolar RNA host genes promoting epithelial-mesenchymal transition lead cancer progression and metastasis. IUBMB Life. 2021 Jun;73(6):825-842.

CÁCERES-DURÁN MÁ, RIBEIRO-DOS-SANTOS Â, VIDAL AF. Roles and Mechanisms of the Long Noncoding RNAs in Cervical Cancer. Int J Mol Sci. 2020; 21(24):9742.

CHU Q, GU X, ZHENG Q, GUO Z, SHAN D, WANG J, ZHU H. Long noncoding RNA SNHG4: a novel target in human diseases. Cancer Cell Int. 2021 Oct 30;21(1):583.

COHEN PA, JHINGRAN A, OAKNIN A, DENNY L. Cervical cancer. Lancet. 2019 Jan 12;393(10167):169-182.

DÍAZ-GONZÁLEZ SDEL M, DEAS J, BENÍTEZ-BOIJSEAUNEAU O, GÓMEZ-CERÓN C, BERMÚDEZ-MORALES VH, et al. Utility of microRNAs and siRNAs in cervical carcinogenesis. Biomed Res Int. 2015; 2015:374924.

FONSECA FV, CORDEIRO MVG, POZZA AC, MAESTRI CA. Cervical Intraepithelial Neoplasia: Analyzing the Disease Present Exclusively in the Endocervical Canal. Rev Bras Ginecol Obstet. 2022 Apr;44(4):385-390.

GONG Y, WAN JH, ZOU W, LIAN GY, QIN JL, WANG QM. MiR-29a inhibits invasion and metastasis of cervical cancer via modulating methylation of tumor suppressor SOCS1. Future Oncol. 2019; 15:1729-1744.

HE J, HUANG B, ZHANG K, LIU M, XU T. Long non-coding RNA in cervical cancer: From biology to therapeutic opportunity. Biomed Pharmacother. 2020; 127:110209.

HILL EK. Updates in Cervical Cancer Treatment. Clin Obstet Gynecol. 2020 Mar;63(1):3-11

INSTITUTO NACIONAL DE CÂNCER JOSÉ ALENCAR GOMES DA SILVA. Estimativa 2023: incidência de câncer no Brasil / Instituto Nacional de Câncer José Alencar Gomes da Silva. – Rio de Janeiro : INCA, 2023.

LI J, YU H, YAO J, JIANG Z, LI Z, CUI X. Integrative Analysis and Experimental Validation Indicated That SNHG17 Is a Prognostic Marker in Prostate Cancer and a Modulator of the Tumor Microenvironment via a Competitive Endogenous RNA Regulatory Network. Oxid Med Cell Longev. 2022 Jul 12;2022:1747604.

LIN G, WU T, GAO X, HE Z, NONG W. Research Progress of Long Non-Coding RNA GAS5 in Malignant Tumors. Front Oncol. 2022 Jun 28;12:846497

NAJAFI S, GHAFOURI-FARD S, HUSSEN BM, JAMAL HH, TAHERI M, HALLAJNEJAD M. Oncogenic Roles of Small Nucleolar RNA Host Gene 7 (SNHG7) Long Noncoding RNA in Human Cancers and Potentials. Front Cell Dev Biol. 2022 Jan 17;9:809345.

PENG WX, KOIRALA P, MO YY. LncRNA-mediated regulation of cell signaling in cancer. Oncogene. 2017;36(41):5661-5667.

QIN Y, SUN W, WANG Z, DONG W, HE L, ZHANG T, ZHANG H. Long Non-Coding Small Nucleolar RNA Host Genes (SNHGs) in Endocrine-Related Cancers. Onco Targets Ther. 2020 Aug 5;13:7699-7717.

RAJAGOPAL T, TALLURI S, AKSHAYA RL, DUNNA NR. HOTAIR LncRNA: A novel oncogenic propellant in human cancer. Clin Chim Acta. 2020; 503:1-18.

SALEH M, VIRARKAR M, JAVADI S, ELSHERIF SB, DE CASTRO FARIA S, BHOSALE P. Cervical Cancer: 2018 Revised International Federation of Gynecology and Obstetrics Staging System and the Role of Imaging. AJR Am J Roentgenol. 2020 May;214(5):1182-1195.

SCHIFFMAN M, CASTLE PE, JERONIMO J, RODRIGUEZ AC, WACHOLDER S. Human papillomavirus and cervical cancer. Lancet. 2007; 370 :890-907.

SHERER MV, KOTHA NV, WILLIAMSON C, MAYADEV J. Advances in immunotherapy for cervical cancer: recent developments and future directions. Int J Gynecol Cancer. 2022 Mar;32(3):281-287.

SHI D, ZHANG C, LIU X. Long noncoding RNAs in cervical cancer. J Cancer Res Ther. 2018;14(4):745-753.

SUNG H, FERLAY J, SIEGEL RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021; 71:209-249.

THOUMI A, BOND SJ, DOTSON ME, KRIEGER M, GARCIA PJ, RAMANUJAM N. Policy Considerations to Promote Equitable Cervical Cancer Screening and Treatment in Peru. Ann Glob Health. 2021 Nov 24;87(1):116.

YANG X, XIE Z, LEI X, GAN R. Long non-coding RNA GAS5 in human cancer. Oncol Lett. 2020 Sep;20(3):2587-2594. doi: 10.3892/ol.2020.11809. Epub 2020 Jul 3.

YOON JH, ABDELMOHSEN K, GOROSPE M. Functional interactions among microRNAs and long noncoding RNAs. Semin Cell Dev Biol. 2014 Oct;34:9-14.

YU Y, HANN SS. Novel Tumor Suppressor lncRNA Growth Arrest-Specific 5 (GAS5) In Human Cancer. Onco Targets Ther. 2019 Oct 11;12:8421-8436.

ZHONG Y, LU Q, QIU W, LUO Y. LINC00636 promotes lymph node metastasis and cervical cancer through targeting NM23. Biosci Rep. 2020; 40(10)

ZIMTA AA, TIGU AB, BRAICU C, STEFAN C, IONESCU C, BERINDAN-NEAGOE I. An Emerging Class of Long Non-coding RNA With Oncogenic Role Arises From the snoRNA Host Genes. Front Oncol. 2020 Apr 7;10:389.

ANEXO 1

NORMAS DA REVISTA REVISTA ASIAN PACIFIC JOURNAL OF CANCER PREVENTION

The Manuscript Main file

Your manuscript is a single file (a text file with embedded figures, tables etc.). You may either prepare your manuscript using a word processing program and save it as a .doc or .rtf file, remembering to insert your figures and tables into the document.

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A Research Article, Systematic Review and Meta-analysis, Methodological Paper, and Case Series, must each contain a structured abstract of approximately 300 words. The structured abstract must have four specified subtitles: Background, Methods, Results, and Conclusion(s). Abstracts are not required for Editorials, Commentaries, Short Communications, or Correspondence.

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In the reference list:

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Rule # 3) Provide the names of all authors if there are 5 or fewer authors.

Rule # 4) If there are more than 5 authors, provide the names of the first three authors, followed by et al.,

Rule # 5) In writing the names of the authors, the rule is to use the last name and then the initials for the first and/or middle names. No period or space between the initials: For example, (Blue AB, Pink B, Green CJ, et al (2000).

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An example for a book: Brown A, Pink B, Black CD, et al (2000). Cancer Prevention. In 'Neoplasia', Eds Blue D and Red E. Asian Pacific Education Press, Bangkok pp 1-10 Numbers 322-4

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- Submit only publication quality high-resolution figures.
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- Figures should be sized to either one-column width (19 picas, 3.25 inches), or two-column width (40 picas, 6.75 inches), as appropriate.
- Figures must be numbered in the text. Number all figures sequentially with Arabic numerals in the order cited in the text.
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