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Molecular alterations and clinical relevance in cervical carcinoma and precursors (Review)

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Abstract. Cervical cancer is one of the most common types of cancer and the fourth leading cause of cancer-related deaths in women. The occurrence and development of cervical cancer is a multifactorial and multilevel process, which usually occurs alongside a continuous high-risk human papillomavirus infection. With further developments in molecular biology and the advancement of sequencing technology, the role of biomarkers in cervical diseases has been gradually recognized. Therefore, it remains a priority to identify key molecular markers that can be used for the screening and triaging of the lesions. In recent years, numerous studies have been conducted in order to identify important markers for cervical diseases. The present review aimed to summarize the molecular alterations and clinical relevance of chromosomal alterations, DNA polymorphisms, the DNA methylation status, histone modifications, and alterations in microRNA and protein expression levels. Accumulating evidence suggests that molecular alterations may reflect the degree and the prognosis of the disease. Although significant progress has been made in the field of cervical cancer research, further samples and experiments are still required to identify crucial molecules.

Contents

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1. Introduction

Cervical cancer is one of the ten most common types of malignancies affecting women. According to the cancer statistics in 2018, there are ~570,000 new cases of cervical cancer and 311,000 deaths due to cervical cancer worldwide each year (1). In addition, Chinese cancer data have estimated ~98,500 cases and 30,500 deaths from cervical cancer, accounting for 17% of cases and 10% of deaths globally. Contrary to the decreasing trend of morbidity in developed countries, the incidence rates of cervical cancer in China have increased significantly since 2000 (2).

The major histological type of cervical cancer is squamous carcinoma of the cervix (SCC). SCC has been confirmed to be caused by high-risk human papillomavirus (HR-HPV) infection. Half of HPV infections are cleared within 6-12 months; however, 10% of HPV infections persist (3). Following HR-HPV infection, cervical cells may undergo the precursor steps of SCC, which are termed squamous intraepithelial lesions (SILs) (4). SILs are classified into low grade SILs (LSILs) and high grade SILs (HSILs), which correspond to the traditional histological classification, known as cervical intraepithelial neoplasia (CIN). CIN1 is the synonym for LSIL, and CIN2 and CIN3 are classified as HSILs (5). The histological diagnosis of CIN is the gold standard to guide subsequent treatment; however, the reproducibility of CIN diagnosis is poor, especially for CIN2, with a diagnostic consistency rate of <50% (6). Moreover, the prognosis of CIN is different. According to a survey, the 10-year transition probability from CIN1 to CIN2 was 4.37%, and from CIN2 to CIN3$^+$ was 25.58% (7). In addition, a recent meta-analysis revealed that the regression rate of CIN2 after a 24-month follow-up was 50% (11 studies, 819/1,470 women) and 60% (4 studies, 638/1,069 women, age <30 years), respectively. Patients with CIN2 who have a plan for future pregnancies can attend screening tests and there is no requirement for immediate treatment (8).

It is imperative to identify molecular markers for the screening and triage of cervical cancer and precancerous lesions. For patients with cervical precancerous lesions,

the identified biomarkers may predict the development of the disease and help to guide subsequent treatments and avoid overtreatment. For patients with cervical cancer, the biomarkers could help to predict the prognosis and potentially be used as therapeutic targets.

For both cervical cancer and precursors lesions, the majority of previous research has investigated the molecular alterations and clinical relevance using PCR, fluorescence *in situ* hybridization, microarrays, ELISAs, western blotting and immunohistochemistry. The present review aimed to provide a summary of the progression of cervical cancer and precursor lesions due to the alteration of chromosomes, DNA polymorphisms, the DNA methylation status, histone modifications, and alterations in the expression levels of microRNAs (miRNAs) and proteins.

2. Chromosomal alterations

The presence of chromosomal aberrations has been confirmed in SCC and its precursors. For example, Policht *et al* (9) reported the gain or loss in copies of 8q24, Xp22, 20q13, 3p14, 3q26 and CEP15 in the cervical tissue of CIN and cancer lesions, and it was further reported that 8q24 and 3q26 were the most useful molecules for detecting HSILs and SCCs. Rodolakis *et al* (10) analyzed the gain of 3q26 in 40 patients and discovered that none of the 3q26(-) progressed to HSILs/CIN2$^+$ after 17.5 months, while 38% of the 3q26(+) patients progressed. The study also revealed that the gain of 3q26 could predict the progression with a negative predictive value (NPV) of 100%. Another meta-analysis indicated a potential association between the gain of 3q26 and disease prognosis (8 studies, 407 patients), with positive predictive values ranging from 50 to 93% and a NPV ranging from 75 to 100% (11). In addition to 3q26, gains in 5p15 were also identified in cervical lesions of increasing severity (12). Based on the above findings, 3q26 was hypothesized to have an important role in cervical cancer and it should be further studied. The details of these molecules are presented in Table I.

3. DNA polymorphisms

DNA polymorphisms are a type of genetic variation that do not change the gene expression levels. Cezar-Dos-Santos *et al* (13) reported that the forkhead box P3 (*FOXP3)* rs3761548 homozygous genotype may be associated with the resistance to HPV infection, while the rs2232365 homozygous genotype (G/G) was a risk factor for HPV infection [odds ratio (OR)=2.10 (95% confidence interval (CI): 1.06-4.15)]. In addition, the Arg72Arg genotype and Arg72 alleles of tumor protein p53 (*TP53*) were also suggested to be related to the susceptibility of HPV infection [OR=1.85 (95% CI: 1.03-3.32) and 1.94 (95% CI: 1.20-3.15), respectively] (14).

The relationship between genetic polymorphisms and cervical cancer susceptibility has also been studied. Chen *et al* (15) suggested that polymerase II polypeptide E (*POLR2E*) may be associated with the susceptibility of cervical cancer and breast cancer. For Uyghur women, the apolipoprotein B mRNA editing enzyme-catalytic polypeptide-like 3G (*APOBEC3G*) and interleukin-1β (*IL1B*) polymorphisms were discovered to be associated with the susceptibility of cervical cancer (16,17). For Han Chinese women, the NAD(P)H: Quinone oxidoreductase 1 (*NQO1*) rs1800566 TT genotype presented with an increased risk of cervical cancer development compared with the CT and CC genotypes (18). Notably, there seems to be ethnic differences in the presence of DNA polymorphisms; for instance, according to a meta-analysis, the cytotoxic T-lymphocyte associated antigen-4 (*CTLA4*) gene rs5742909 polymorphism was related to the susceptibility of cervical cancer in Asians, but it had little association with cervical cancer in Caucasians (19). Similarly, genetic polymorphisms, such as in the deoxyuridine triphosphatase (*DUT*) gene, were also discovered to be associated with HSIL susceptibility (20). Thus, DNA polymorphisms have been suggested to serve a predictive role for the susceptibility of cervical lesions. Predicting the early occurrence of cervical cancer can help prevent its occurrence, thus it is worthy of research. The details of these findings are presented in Table II.

4. DNA methylation

Sakane *et al* (21) investigated the methylation of distal-less homeobox 4 (*DLX4*) and SIM bHLH transcription factor 1 (*SIM1*) in LSILs; significant differences were identified in the methylation frequency of *DLX4* and *SIM1* between LSILs that persisted for >1 year and LSILs that progressed to HSILs within a year (P=0.044 and P=0.005, respectively). LSIL cases with *SIM1* methylation were identified to progress to HSILs faster compared with DNA methylation-negative cases (P=0.033). According to a meta-analysis of 1,055 patients in 7 studies, paired box gene 1 (*PAX1*) methylation was also discovered to be a protective factor for CIN1 to CIN2/3 progression and CIN2/3 to cervical cancer progression, demonstrating an OR of 0.09 and 0.16, respectively (22). Through studying plasma samples, the methylation of maternally expressed 3 (*MEG3*) in CIN3 and cervical cancer was identified to be significantly increased compared with that in healthy controls, exhibiting an OR of 13.033 and 17.100, respectively. In addition, the methylation status of *MEG3* was increased in cervical cancer tissues compared with normal tissues, which indicated that the methylation status of *MEG3* may have a diagnostic value in plasma and tissues (23).

In another study, the methylation patterns of 15 genes in the normal cervix and CIN1-3 cervixes were analyzed using quantitative methylation-specific PCR. The methylation of hsa-miR-124-2, SRY-box transcription factor 1 (*SOX1*), telomerase reverse transcriptase (*TERT*) and LIM homeobox transcription factor 1-α (*LMX1A*) genes were discovered to be independent predictors associated with the diagnosis of high-grade cervical lesions, exhibiting ORs of 5.1, 2.8, 2.2, 2.0, respectively (24). Verlaat *et al* (25) discovered that the methylation of growth hormone secretagogue receptor (*GHSR*), somatostatin (*SST*) and Zic family member 1 (*ZIC1*) were also associated with gain in 3q and an increased severity of cervical lesions (P<0.005). Finally, De Strooper *et al* (26) followed 1,040 HPV-positive women for 14 years and discovered that women with negative family with sequence similarity 19 (chemokine (C-C)-motif)-like)-member A4 (*FAM19A4)/miR-124-2* methylation had a lower risk of cervical cancer. The findings described above are presented in Table III.

Table I. Chromosomal alterations in cervical disease.

Name	Population (Refs.)	Sample	Cases	Methods	Potential role	Alteration
8q24						↑
3q26	USA (9)	NC, CIN, SCC	136	FISH	Diagnosis	↑
3q26	Slovakia (12)	NC, LSIL, HSIL, SCC/AC	131	FISH	Diagnosis	↑
5p15						↑
3q26	Greece (10)	ASCUS/LSIL	40	FISH	Prognosis	-
3q26	Norway (11)	CIN2/3	19	FISH	Prognosis	-

NC, normal cervix; CIN, cervical intraepithelial neoplasia; SCC, squamous carcinoma of cervix; ASCUS, atypical squamous cells of undetermined significance; LSIL, low grade squamous intraepithelial lesion; HSIL, high grade squamous intraepithelial lesion; AC, adenocarcinoma; ASC, adenosquamous carcinoma; FISH, fluorescence *in situ* hybridization. ↑, indicates that the molecule is upregulated in cervical diseases. -, indicates that the amount of molecules was not compared in different tissues.

Table II. DNA polymorphisms in cervical disease.

Name	Variation	Population (Refs.)	Cases	Methods
Association with HPV infection				
FOXP3	rs3761548, rs2232365	Brazil (13)	426	PCR
TP53	rs1042522	Kyrgyz (14)	205	PCR
Association with cancer susceptibility				
POLR2E	rs3787016	China (15)	884	PCR
APOBEC3G	rs5757465	Uygur (16)	529	First-generation
IL1B	rs1143627	Uygur (17)	569	PCR
NQO1	rs1800566	China (18)	1,018	PCR
CTLA4	rs5742909	Asian (19)	8,507	Meta[a]
DUT	rs3784619, rs11637235	China (20)	2,000	PCR
Association with CIN3 susceptibility				
FOXP3	rs3761548	Brazil (13)	426	PCR
DUT	rs3784619, rs11637235	China (20)	2,000	PCR

FOXP3, forkhead box P3; *TP53*, tumor protein p53; *POLR2E*, polymerase II polypeptide E; *APOBEC3G*, apolipoprotein B mRNA editing enzyme-catalytic polypeptide-like 3G; *IL1B*, interleukin-1β; *NQO1*, NAD(P)H: Quinone oxidoreductase 1; *CTLA4*, cytotoxic T-lymphocyte associated antigen-4; *DUT*, deoxyuridine triphosphatase; PCR, polymerase chain reaction. [a]Meta-analysis study.

5. Histone modifications

Histone modifications involve processes in which histones undergo acetylation, methylation or other modifications under the action of related enzymes. Upon analyzing the expression levels of histone H3 acetyl K9 (H3K9ac) and histone H3 tri methyl K4 (H3K4me3) in cervical cancer, Beyer *et al* (27) discovered that both histones were related to the clinicopathological variables of patients. In addition, the staining intensity of H3K9ac was also identified to be associated with the 10-year survival rate. These findings revealed the important role of histone acetylation and methylation in cervical cancer. Zhang *et al* (28) also discovered that HPV 18 E6/E7 enhanced the transcriptional activity of enhancer of zeste homolog 2 (*EZH2*), thereby enhancing the expression levels of histone 3 tri methyl K27 (H3K27me3) and exerting a positive effect on the development of cervical cancer. Polycomb repressive complex 2 (PRC2) can also catalyze the methylation of histones, thereby inhibiting gene expression. Shi *et al* (29) identified C10ORF12 as an interactor of PRC2, which was found to positively regulate H3K27me3 modifications. At present, inhibitors for enzymes controlling histone modifications have been developed and are being used in clinical cancer treatment (30). However, to the best of our knowledge, related studies in cervical cancer are rare. Therefore, further research into histone modifications in cervical cancer is required.

6. miRNA alterations

Zeng *et al* (31) compared the expression levels of nine miRNAs in normal cervical, LSIL, HSIL and cervical cancer tissues; the results revealed that in cervical cancer, miR-218 expression levels were downregulated by 0.175-fold (P=0.002), while miR-21 expression levels were upregulated by 5.677-fold (P=0.001) compared with the normal tissues. Zhu *et al* (32) discovered that the upregulation of miR-21-5p

Table III. DNA methylation in cervical disease.

Name	Population (Refs.)	Sample	Cases	Methods	Alteration
DLX4					↑
SIM1	Japan (21)	NC, CIN, SCC	113	PCR, IHC	↑
PAX1	Meta[a] (22)	NC, CIN, SCC/AC	1,055	Meta[a]	↓
MEG3	China (23)	NC, CIN, SCC, AC	168	MSP	↑
hsa-miR-124-2	Brazil (24)	NC, CIN	447	PCR	↑
SOX1					↑
TERT					↑
LMX1A					↑
GHSR	The Netherlands (25)	NC, CIN, SCC	233	NGS	↑
SST					↑
ZIC1					↑
FAM19A4/miR-124-2	The Netherlands (26)	LSIL	1,040	PCR	-

DLX4, distal-less homeobox 4; *SIM1*, SIM bHLH transcription factor 1; *PAX1*, paired box gene 1; *MEG3*, maternally expressed 3; *SOX1*, SRY-box transcription factor 1; *TERT*, telomerase reverse transcriptase; *LMX1A*, LIM homeobox transcription factor 1-α; *GHSR*, growth hormone secretagogue receptor; *SST*, somatostatin; *ZIC1*, Zic family member 1; *FAM19A4*, family with sequence similarity 19 (chemokine (C-C)-motif)-like)-member A4; NC, normal cervix; CIN, cervical intraepithelial neoplasia; SCC, squamous carcinoma of cervix; AC, adenocarcinoma; PCR, polymerase chain reaction; IHC, immunohistochemistry; NGS, 'next-generation' sequencing technology; MSP, methylation-specific polymerase chain reaction. [a]Meta-analysis study. ↑, indicates that the molecule is upregulated in cervical diseases; ↓, indicates that the molecule is downregulated in cervical diseases; -, indicates that the amount of molecules was not compared in different tissues.

expression levels and the downregulation of miR-34a expression levels were associated with the severity of cervical lesions (P<0.05). In addition, miR-409-3p was negatively associated with E6 mRNA, and subsequent cell experiments revealed that it exerted an inhibitory effect on cervical cancer cells (33).

Recently, numerous studies have focused on the expression levels of miRNAs and their target genes in cervical cancer. Jin *et al* (34) compared the expression levels of miR-612 in normal and cancerous cervical tissues and cells, and discovered that they were downregulated in cancer tissues and cells, and that the target of miR-612 was nin one binding protein (*NOB1*). Zhao *et al* (35) reported that miR-15a-5p expression levels were upregulated in cervical cancer, and TP53 regulated inhibitor of apoptosis 1 (*TP53INP1*) was identified as the target gene. In fact, numerous miRNAs have been discovered to be downregulated in cervical cancer, including miR-889-3p (36), miR-299-3p (37), miR-140-3p (38), miR-505-5p (39), miR-877 (40), miR-636 (41), miR-144-3p (42), miR-139-5p (43), miR-126 (44), miR-138 (45), miR-526b (46), miR-432 (47), miR-543 (48) and miR-503 (49). Conversely, miRNAs that have been identified to be upregulated in cervical cancer include miR-93-5p (50) and miR-150-5p (51).

In addition, the detection of miRNA in the blood has also been suggested as a feasible method to diagnose cervical diseases. For example, the expression levels of miR-3142 in the serum of patients with cervical cancer were reported to be significantly upregulated compared with these levels in healthy individuals, and the high expression levels of miR-3142 were associated with a poor prognosis (52). In addition, Zheng *et al* (53) performed miRNA sequencing of plasma samples and screened out two significant miRNAs, let-7d-3p and miR-30d-5p; these two miRNAs were discovered to be able to distinguish between $CIN1^-$ and $CIN2^+$ lesions [area under the curve (AUC)=0.828].

The details of these studies described above are presented in Table IV. It is worth mentioning that previous studies investigating the therapeutic ability of miRNAs in treating cancer have been performed, such as for the treatment of liver and breast cancer (54). However, there still remains a long way to go for the clinical application of miRNAs for the treatment of cervical cancer.

7. Protein alterations

The effect of the p16INK4a (p16), Ki-67 and cytokeratin 7 (CK7) proteins have been studied in cervical cancer and precancerous lesions. p16 is a tumor-suppressor protein that serves an important role in cell cycle regulation by decelerating the progression of cells from the G_1 phase to S phase. Ki-67 is a protein that is present during the active phase of the cell cycle and is involved in the proliferative activity of tumors. High p16 expression levels and >50% of Ki-67 expression in CIN2 lesions was discovered to have a higher probability of progressing to CIN3 and cancerous lesions (P<0.001), with a hazard ratio of 2.58 and 2.84, respectively (55). Another study demonstrated that all of the HSIL/CIN2 patients with p16-negative expression had either regressed to normal or CIN1 tissue during the 12 months of follow-up, while both persistent and progressive CIN2 lesions were p16-positive (56). Therefore, these findings suggested that p16 and Ki-67 may be used to predict the outcome of CIN2.

While it is controversial to predict the outcome of CIN1, a follow-up study of an average of 28 months revealed that p16 staining had limited value in predicting the progression of LSILs to higher-grade lesions (57). In addition, HPV16/18 was discovered

Table IV. miRNAs in cervical disease.

Name	Population (Refs.)	Sample	Cases	Methods	Target gene	Alteration
miR-612	China (34)	NC, CC	52	PCR	*NOB1*	↓
miR-15a-5p	China (35)	NC, CC	30	PCR	*TP53INP1*	↑
miR-889-3p	China (36)	NC, CC	49	PCR	*FGFR2*	↓
miR-299-3p	China (37)	Cell lines	0	PCR	*TCF4*	↓
miR-140-3p	China (38)	NC, CC	44	PCR	*RRM2*	↓
miR-505-5p	China (39)	NC, CC	60	PCR	*CDK5*	↓
miR-877	China (40)	NC, CC	57	PCR	*MACC1*	↓
miR-636	China (41)	NC, CC	40	PCR	*BCL2, CDK6*	↓
miR-144-3p	China (42)	NC, CC	23	PCR	*MAPK6*	↓
miR-139-5p	China (43)	NC, CC	40	PCR	*TCF4*	↓
miR-126	China (44)	NC, CC	30	PCR	*ZEB1*	↓
miR-138	China (45)	Cell lines	0	PCR	*H2AX*	↓
miR-526b	China (46)	NC, SCC, AC	85	PCR	*PBX3*	↓
miR-432	China (47)	NC, CC	47	PCR	*FN1*	↓
miR-543	China (48)	NC, SCC, AC	69	PCR	*TRPM7*	↓
miR-503	China (49)	NC, CC	52	PCR	*AKT2*	↓
miR-93-5p	China (50)	NC, CIN, CC	328	PCR	*BTG3*	↑
miR-150-5p	China (51)	Cell lines	0	PCR	*SRCIN1*	↑

NC, normal cervix; CIN, cervical intraepithelial neoplasia; SCC, squamous carcinoma of cervix; CC, cervical cancer; AC, adenocarcinoma; PCR, polymerase chain reaction; FISH, fluorescence *in situ* hybridization. ↑, indicates that the molecule is upregulated in cervical diseases. ↓, indicates that the molecule is downregulated in cervical diseases.

to be more capable of predicting LSIL progression compared with other HR-HPVs; however, there was no association identified between p16/Ki-67 staining and prognosis (58). Therefore, further research is required for p16 and Ki67. In addition, other previous p16-related research has been conducted (59-61).

Cytokeratin 7 (CK7) is a squamocolumnar junction-related immunomarker. Paquette *et al* (62) identified that CK7-positive LSILs progressed with more ease to HSILs compared with negative CK7 LSILs (32.0 vs. 11.1%; P=0.05). Mills *et al* (63) proved that high levels of CK7 staining were associated with the progression of CIN1 to CIN2 (OR=2.8; P=0.021) and to CIN3 (OR=5.7; P=0.018). Cao *et al* (64) also reported the role of CK7 in CIN.

Wu *et al* (65) determined that the expression levels of cancerous inhibitor of PP2A (CIP2A) increased alongside the development of cervical lesions. CIP2A could bind to the oncogene H-Ras and activate the MEK/ERK signaling pathway, which subsequently promoted epithelial-mesenchymal transition (EMT) in cervical cancer progression. Human discs large tumor suppressor (DLG1) is a component of the Scribble polarity complex; through a 2-year follow-up study, Cavatorta *et al* (66) identified that the cases progressing from LSILs to HSILs had diffuse DLG1 expression, and that LSILs with a DLG1 staining pattern similar to normal tissue were more likely to regress. Myosin IB (MYO1B) is a member of class I myosin, which was discovered to participate in the cell migration of zebrafish embryonic cells. In addition, MYO1B expression levels were upregulated in squamous cervical cancer and cervical cancer cell lines, where it served a role in cancer cell proliferation, migration and invasion (67).

A previous study investigating the expression levels of multiple proteins in exfoliated cervical cells indicated that the expression levels of Sialyl-Lewis A in cervical cancer were significantly downregulated compared with normal and CIN lesions (P<0.01). In addition, the expression of HPV L1 and p53 in cervical cancer were increased compared with normal and CIN lesions (P<0.05) (68). Compared with normal cervical tissue, the expression of T lymphoma invasion and metastasis 1 (Tiam1) was significantly increased in CIN and cervical cancer (P<0.05 and P<0.01, respectively), and the upregulated expression levels of Tiam1 were discovered to be associated with a poor prognosis in patients with cervical cancer. In addition, Tiam1 promoted the proliferation and migration of cancer cells by activating EMT (69). Mizushima *et al* discovered that following the development of normal cervical tissue to CIN, as the severity of the lesions increased, the expression of atypical protein kinase C λ/ι (aPKCλ/ι) also increased. In fact, aPKCλ/ι overexpression and nuclear localization were identified as independent factors for CIN1 progression, with hazard ratios of 4.26 (P=0.007) and 3.59 (P=0.019), respectively (70). Hester *et al* also discovered that prostaglandin E2-receptor 3 (EP3) expression was decreased with increasing grades of cervical lesions (from normal to CIN1-3; P<0.05). Notably, the proportion of EP3-positive cells in progressed CIN2 was decreased compared with in regressed CIN2 (P=0.04) (71).

In recent years, numerous studies have been conducted to determine the relationship between protein levels in the blood and cervical diseases. Sawada *et al* (72) found that patients with cervical cancer with high levels of vascular endothelial

Table V. Protein alterations in cervical disease.

Name	Population (Refs.)	Sample	Cases	Methods	Alteration
Potential diagnosis markers					
p16	Italy (59)	CIN1/3	66	IHC	↑
p16	China (61)	NC, CIN, SCC	254	WB	↑
CK7	USA (62)	NC, CIN, SCC	326	IHC	↑
CK7					↓
HPV L1	China (64)	LSIL, HSIL	100	IHC	↑
CIP2A	China (65)	NC, CIN, SCC	105	PCR, IHC, WB	↑
MYO1B	China (67)	NC, CIN, SCC	335	IHC	↓
SLeA	Korea (68)	NC, CIN, CC	146	ELISA, WB, IP	↑
HPV L1					↑
p53					↑
Tiam1	China (69)	NC, CIN, CC	298	IHC	↑
aPKCλ/ι	Japan (70)	NC, CIN	205	IHC	↑
EP3	Germany (71)	NC, CIN	124	IHC	↓
RAP1	Brazil (74)	NC, CIN	183	IHC	↑
COX-2					↑
EGFR	Brazil (75)	NC, CIN, SCC	412	IHC	↑
NCL	China (76)	NC, CIN, SCC	175	IHC	↑
HBXIP	China (77)	NC, CIN, SCC	243	IHC	↑
ERK1/2	China (78)	NC, CIN, SCC	176	PCR, IHC	↑
A3G	Japan (79)	NC, CIN, SCC	34	PCR, IHC	↑
HPV 16					↑
hnRNP K	China (80)	NC, CIN	204	FH, WB	↑
MFN2	Korea (81)	NC, CIN, SCC	191	IHC	↑
ADAR1	China (82)	NC, CIN, SCC	303	IHC	↑
Geminin	China (83)	NC, CIN	95	IHC	↑
SIRT1	USA (84)	CIN, SCC	101	IHC	↑
Gankyrin	China (85)	NC, CIN, SCC	76	IHC	↑
Potential prognosis markers for CIN1					
HPV16/18	Spain (58)	LSIL	200	IHC	-
HPV L1	Italy (59)	CIN1/3	66	IHC	↓
p16					
HPV L1	Japan (60)	CIN	199	PCR, IHC	-
CK7	USA (62)	NC, CIN, SCC	326	IHC	↑
CK7	USA (63)	CIN1	517	IHC	-
CK7					↑
HPV L1	China (64)	LSIL, HSIL	100	IHC	↓
DLG1	Argentina (66)	LSIL	30	IHC	-
aPKCλ/ι	Japan (70)	NC, CIN	205	IHC	↑
RAP1	Brazil (74)	NC, CIN	183	IHC	↑
Potential prognosis markers for CIN2					
p16/Ki-67	Japan (55)	CIN2	122	IHC	-
p16	Spain (56)	HSIL/CIN2	96	IHC	-
p16					
HPV L1	Japan (60)	CIN	199	PCR, IHC	-
EP3	Germany (71)	NC, CIN	124	IHC	↓

NC, normal cervix; CIN, cervical intraepithelial neoplasia; SCC, squamous carcinoma of cervix; CC, cervical cancer; LSIL, low grade squamous intraepithelial lesion; HSIL, high grade squamous intraepithelial lesion; IHC, immunohistochemistry; PCR, polymerase chain reaction; WB, western blot analysis; ELISA, enzyme linked immunosorbent assay; IP, immunoprecipitation; FH, flow-through hybridization; ↑, indicates that the molecule is upregulated in cervical diseases; ↓, indicates that the molecule is downregulated in cervical diseases; -, indicates that the amount of molecules was not compared in different tissues.

growth factor A (VEGF-A) and vascular endothelial growth factor receptor 2 (VEGFR-2) in the serum had a poor prognosis. Maestri *et al* (73) discovered that the serum levels of MBL-associated serine proteases (MASP)-2, MASP-1 and MAP-19 in patients with cervical cancer were significantly upregulated compared with in CIN and normal tissues ($P<0.0001$, $P=0.012$, $P=0.025$, respectively). These findings indicated that detecting the levels of specific proteins in the blood may help diagnose and predict the prognosis of cervical diseases.

Other proteins discovered to be involved in cervical cancer and precursors include RAS proximate 1 (RAP1) (74), cyclooxygenase-2 (Cox-2), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor-2 (ERBB-2) (75), nucleolin (NCL) (76), hepatitis B virus X-interacting protein (HBXIP) (77), extracellular signal-regulated kinas 1/2 (ERK1/2) (78), APOBEC3G (79), heterogeneous nuclear ribonucleoproteins K (hnRNP K) (80), mitofusin-2 (MFN2) (81), RNA-dependent adenosine deaminase (ADAR1) (82), geminin (83), sirtuin 1 (SIRT1) (84) and gankyrin (85), among others. The details of these molecules are listed in Table V.

8. Conclusion

A significant amount of research has accumulated regarding the possible development of biomarkers for the early diagnosis of cervical lesions and the risk assessment of precursors. The development of cervical cancer is a multifactorial process; the transition from normal cervix tissue to precursors/cervical cancer is associated with chromosomal alterations, DNA polymorphisms, the DNA methylation status, histone modifications, and alterations to miRNA and protein expression levels. The majority of the experimental studies are conducted using cervical tissues and cells, while a small number of specimens are studied in the blood of patients. Since liquid biopsies represent a detection method with demonstrated diagnostic and monitoring value for cancer, which exert little harm to the body due to the non-invasive nature, they warrant further research in the future. Although there has been significant progress in the field of cervical cancer research, the identification of important molecules that could help predict the progression and prognosis of cervical cancer are still required. However, future studies require more samples and improved experimental designs.

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Author's contributions

JS and YX wrote the manuscript and constructed the tables. LS and QH designed and revised the manuscript. JS, YX, LS and QH were responsible for the submission of the manuscript and the final approval of the version to be published. All authors were involved in the literature search and review.

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Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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