Dysregulated expression of circular RNAs serve as diagnostic and prognostic markers in ovarian and cervical cancer

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Introduction: Recent studies have reported a connection between non-coding RNAs such as circular RNAs (circRNAs) and the prognosis of various cancers. However, the mechanism of circRNA in ovarian cancer and cervical cancer has not been consistent. We evaluated the diagnostic and prognostic roles of circRNAs in ovarian and cervical cancer by meta-analysis.

Methods: Pooled hazard ratios with 95% confidence intervals were to estimate overall survival. Diagnostic efficacy was estimated by sensitivity, specificity and area under curve.

Results: By searching PubMed, Embase, the Web of Science databases, and other sources, we obtained a total of 22 studies with 2059 patients from Asia population. High expression levels of oncogenic circRNAs were significantly associated with poor prognoses both in ovarian and cervical cancer. However, elevated expression levels of tumor-suppressor circRNAs were linked with favorable survival time in ovarian cancer. As for diagnostic role, the area under the curve value in ovarian cancer and cervical cancer is 0.89 and 0.93, respectively.

Conclusions: CircRNAs have the prospect of becoming a promising biomarker for diagnosis and prognosis of ovarian and cervical cancer. Accordingly, circRNAs might be novel indicators and targets of therapy for ovarian and cervical cancer.

Abbreviations: AUC = area under the ROC curve, CI = confidence interval, HR = hazard ratio, OS = overall survival, SEN = sensitivity, SPE = specificity.

Keywords: cervical cancer, CircRNA, diagnostic, ovarian cancer, prognostic

1. Introduction

Ovarian and cervical cancer are the 2 most common tumors in females.\cite{11} Among the tumor-related causes of death in young women, cervical cancer ranks second.\cite{2} Approximately 527,600 new cases and 265,700 mortalities annually and showing an increasing trend with cervical cancer.\cite{12} Besides, ovarian cancer was the 7th most common cancer in 2012 and it was predicted that the number of deaths due to ovarian cancer will increase to 254,000 in 2035 by the Globocan study.\cite{3,4}

CircRNAs are a special kind of endogenous noncoding RNAs that have connected 3’ and 5’ ends that form a closed covalent ring structure through the cyclization of exons or introns. They are also competitive RNAs that, along with long-chain non-coding RNAs, coregulate microRNAs.\cite{5-8} CircRNA participates in the growth and development of cancer, diabetes, nervous system disorders, cardiovascular diseases, and other diseases through various biological roles, such as sponge action, protein translation, and binding protein action.\cite{9-12} In recent years, more and more researchers have found that circRNA plays an important role in the development of ovarian and cervical cancer. However, no consistent results have been obtained regarding the mechanism of circRNA in the 2 cancers.\cite{13-26}

Through the study of Zhao et al.\cite{27} oncogenic human papillomaviruses (HPVs) produce circRNA, which inhibits cancer cell growth both in vitro and in tumor xenografts. And, Guan et al.\cite{28} reported circPUM1 promoted tumorigenesis and progression of ovarian cancer through sponge miR-615–5p and miR-6735-5p. Enhanced understanding of the role of...
circRNAs in ovarian and cervical cancer survival will provide more accurate prognostic information and could improve clinical decision-making in trial design and cancer treatment. Accordingly, we conducted this meta-analysis based on plenty of original documents to identify the role of circRNAs in ovarian and cervical cancer.

2. Methods

2.1. Ethics statement

All analyses were based on previously published studies, this article does not contain any studies with human participants or animals performed by any of the authors; thus, ethical approval and patient consent are not applicable.

2.2. Search strategy

Based on the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group and Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement,[29] we searched the Web of Science, EMBASE, PubMed, Cochrane library and CNKI databases up to August 1, 2020. The searching items were: “circRNA,” “circular RNA,” “hsa circ,” “gynecological cancer,” “ovarian cancer,” “oophoroma,” “carcinoma of the ovary,” “met rocarcinoma,” and “cervical cancer.” To avoid missing documents, we manually screened the reference lists of the retrieved articles.

2.3. Eligibility criteria

Eligible articles conformed to the following criteria: the subjects were ovarian cancer or cervical patients confirmed by histopathological diagnosis and the clinical data were complete; the article evaluated the relationship between circRNA expression, clinico-pathological features, diagnosis and prognosis; and (3) it was a case-control study. The exclusion criteria were: the subjects of the study were not human; the publication was not a primary research publication (eg, a review, correspondence, repeated publication, conference summary), there were no data available in the article.

2.4. Quality assessment

The quality of primary diagnostic accuracy studies was assessed by the QUADAS-2 tool. The QUADAS tool consists of 4 key domains, including patient selection, index test, reference standard, and flow of patients. The answer to risk for bias could be rated as “no” (0 points), “yes” (1 point), or “unclear” (0 points). The Newcastle-Ottawa Scale was used to evaluate the quality of case-control studies from three aspects: selection, comparability, and results. Publications that were rated <6 points were considered of low quality; high quality was ≥6 points.

2.5. Data extraction

Two researchers (LFY, WXR) separately evaluated the suitability of all retrieved studies and extracted the relevant data. The 2 researchers contacted a third researcher (WF) when there was a disagreement. The following data were extracted: title, first author, ethnicity, year, sample type, patient size, circRNA signature, follow-up (months), TNM stage, expression status, detection methods, sensitivity (SEN), specificity (SPE), cutoff value setting, pooled hazard ratios (HRs), overall survival (OS), disease-free survival, and their corresponding 95% confidence intervals (CIs). When HRs and 95% CIs could not be extracted directly, we applied the methods described by Parmar et al[32] and Tierney et al[11] to estimate the values from the Kaplan-Meier curves in the articles.

2.6. Statistical analysis

HRs and 95% CIs were used to estimate OS. Sensitivity, SPE, and area under the curve (AUC) were involved in the diagnostic meta-analysis. Heterogeneity was assessed by the $\chi^2$ test and expressed by the I$^2$ index and was judged to be significant if the I$^2$ value was >50%. We used SEN analyses to investigate potential sources of heterogeneity. Publication bias was evaluated quantitatively using Deeks funnel plot, Begg tests, and Egger tests. Statistical analyses were performed using Revman 5.3 and Stata 15.1 software (Stata Corporation, College Station, TX).

3. Results

3.1. Selection of studies

A total of 398 articles were initially obtained from the databases and other sources based on keywords (Fig. 1). Among these articles, 229 duplicated articles were removed, and 169 articles remained. By looking through titles and abstracts, 55 articles were left for further full-text review. We then reviewed the full texts of these articles carefully and excluded an additional 33 articles. One article has 2 studies independently.[34] Finally, 22 studies (20 articles)[13–26,34–39] were included in this meta-analysis, including 6 for diagnosis,[34–38] and 16 for prognosis.[13–26,34,39]

3.2. Characteristics of included studies and quality assessment

The study characteristics are shown in Tables 1 and 2. A total of 2059 patients with ovarian and cervical cancer from Asia were collected from the 22 included studies.[13–26,34–39] The article incorporated two types of gynecological tumors including ovarian tumors and cervical tumors. The publication years ranged from 2017 to 2020. The follow-up period varied from 48 to 110 months. With the QUADAS-II criteria, the scores of all diagnostic researches were ≥4 (see Fig. 1, Supplemental Content, http://links.lww.com/MD/G413, which illustrates the Study quality assessed by the QUADAS II tool). Assessed by the Newcastle-Ottawa Scale, the points of the prognostic trials were ≥6 (see Table 3, Supplemental Content, http://links.lww.com/MD/G415, which illustrates the study quality assessed via the Newcastle-Ottawa Scale checklist.). The results indicated that all of the articles are of high quality.

3.3. Functions and mechanisms of circRNA in ovarian and cervical cancer

3.3.1. CircRNA in ovarian cancer. The expression and mechanisms of circRNAs in ovarian cancer are presented in Table 3. Several circRNAs (circ0004390, circHIPK3, circ-PIP5K1A, circUBAP2, circ-ABCBI0, hsa_circ_0051240, circ FAM53B) exert their oncogenic roles in ovarian cancer cells.[13,14,18,19,21,26,39] For instance, circPIP5K1A acts as a sponge of miR-661 to promote ovarian cancer progression via regulation of IGFBP5. Nevertheless, Various circRNAs (such as...
circ-ITCH, circPLEKHM3, circRNA_100395, circLARP4) have been found to inhibit the proliferation of ovarian cancer cells by acting as miRNA sponges.\cite{16,17,20,22} CircPLEKHM3 suppresses the proliferation and migration of ovarian cancer cells by sponging miR-9 to regulate BRCA1, DNAJB6, and KLF4.

3.3.2. CircRNA in cervical cancer. The included studies\cite{15,23–25,34} showed that the circRNA-miRNA-mRNA regulatory networks made key functions in managing cervical cancer oncogenesis. Various circRNAs (such as circSLC26A4, circ-ATP8A2) promoted the oncogenesis of cervical cancer by increasing the downstream mRNAs, including HOXA1 and EGFR via sponging miRNAs\cite{15,23} (Table 3). In addition, overexpression of circRNA induces cancer cell invasion and metastasis by activating the molecular pathway. For example, circCLK3 enhanced cell proliferation, migration and invasion through sponging miR-320a and promoting FoxM1 expression.\cite{24}

3.4. Prognostic value of circRNA on ovarian and cervical cancer

3.4.1. Ovarian cancer studies. Eleven studies were included in the meta-analysis of ovarian cancer.\cite{13–24,32,37–39} Elevated expression of tumor suppressor circRNAs was related to a favorable prognosis (HR$=0.34$, 95% CI: 0.23–0.50, $P < .001$) (Fig. 2 A). A fixed-effect model was applied because there was low heterogeneity ($I^2 = 0\%$, $P = .831$). Conversely, high expression of

### Table 1

| Study            | Year | circRNA signature | Cancer type      | Case | Control | Detection methods | Expression status | Sen  | Spe  | AUC  |
|------------------|------|-------------------|------------------|------|---------|-------------------|-------------------|------|------|------|
| Wang et al\cite{38} | 2017 | hsa_circ_0101996  | Cervical cancer  | 87   | 55      | qRT-PCR           | Upregulated       | 0.897| 0.836| 0.906|
| Wang et al\cite{38} | 2017 | hsa_circ_0101119  | Cervical cancer  | 87   | 55      | qRT-PCR           | Upregulated       | 0.701| 0.927| 0.887|
| He et al\cite{34}  | 2020 | circ_0018289      | Cervical cancer  | 96   | 96      | qRT-PCR           | Upregulated       | 0.807| 0.896| 0.907|
| Pei et al\cite{36} | 2020 | hsa_circ_0013958  | Ovarian cancer   | 45   | 45      | qRT-PCR           | Upregulated       | 0.800| 0.911| 0.912|
| Wang et al\cite{37} | 2019 | circSETDB1        | Ovarian cancer   | 32   | 28      | qRT-PCR           | Upregulated       | 0.783| 0.733| 0.83  |
| Hu et al\cite{35}  | 2019 | circBNC2          | Ovarian cancer   | 83   | 83      | qRT-PCR           | Downregulated     | 0.952| 0.855| 0.923|

AUC = area under the ROC curve, qRT-PCR = quantitative real-time polymerase chain reaction, sen = sensitivity, spe = specificity.
tumor-promoter circRNAs was linked with an unfavorable prognosis (HR = 2.35, 95% CI: 1.71–3.21, P < .001) (Fig. 2B). There was no significant heterogeneity (I² = 0%, P = 1.000), so the fixed-effect model was performed for this analysis as well.

3.4.2. Cervical cancer studies. Five studies were included in the analysis of the effect of circRNA on ovarian cancer overall survival. The results showed that high expression of Cervical cancer tumor-promoter circRNAs was associated with poor survival time (HR = 2.53, 95% CI: 1.72–3.73, P < .001) (Fig. 2C). No significant heterogeneity was found across the studies (I² = 0%, P = .931). The relation between tumor suppressor circRNA and overall survival failed to obtain due to the lack of suitable original studies.

### Table 2
Main characteristics of studies for prognosis analysis.

| Study            | Ethnicity | Year | Sample type | Patient size | CircRNA signature | Follow-up (mo) | Cancer type      | Expression status | OS HR (95% CI) | Detection methods |
|------------------|-----------|------|-------------|--------------|-------------------|---------------|-----------------|-------------------|-----------------|------------------|
| Xu et al.        | Asian     | 2020 | tissue      | 60           | Circ0004390       | 50            | Ovarian cancer  | Upregulated      | 2.55 (1.02-6.41) | qRT-PCR           |
| Liu et al.       | Asian     | 2018 | tissue      | 69           | circHIPK3        | 80            | Ovarian cancer  | Upregulated      | 2.18 (1.06-3.78) | qRT-PCR           |
| Luo et al.       | Asian     | 2018 | tissue      | 77           | Circ-ITCH        | 50            | Ovarian cancer  | Downregulated    | 0.20 (0.06-0.65) | qRT-PCR           |
| Sun et al.       | Asian     | 2019 | tissue      | 25           | circPIPSK1A      | 70            | Ovarian cancer  | Upregulated      | 2.03 (0.41-10.02)| qRT-PCR           |
| Zhang et al.     | Asian     | 2019 | tissue      | 86           | CircPLEKH3M3     | 110           | Ovarian cancer  | Downregulated    | 0.38 (0.16-0.94) | qRT-PCR           |
| Song et al.      | Asian     | 2019 | tissue      | 24           | circUBAP2        | 80            | Ovarian cancer  | Upregulated      | 2.39 (1.04-5.46) | qRT-PCR           |
| Li et al.        | Asian     | 2020 | tissue      | 60           | CircRNA_100395   | 67            | Ovarian cancer  | Downregulated    | 0.37 (0.17-0.79) | qRT-PCR           |
| Chen et al.      | Asian     | 2019 | tissue      | 103          | Circ-ABCB10      | 60            | Ovarian cancer  | Upregulated      | 2.99 (1.29-6.94) | qRT-PCR           |
| Zhang et al.     | Asian     | 2019 | tissue      | 33           | hsa_circ_0051240 | 60            | Ovarian cancer  | Upregulated      | 2.21 (0.59-8.24) | qRT-PCR           |
| Zou et al.       | Asian     | 2018 | tissue      | 78           | circLARP4        | 70            | Ovarian cancer  | Downregulated    | 0.35 (0.20-0.66) | qRT-PCR           |
| Sun et al.       | Asian     | 2019 | tissue      | 54           | circ-FAM53B      | 60            | Ovarian cancer  | Upregulated      | 2.18 (1.18-4.05) | qRT-PCR           |
| He et al.        | Asian     | 2020 | tissue      | 192          | circ_0018289     | 48            | Cervical cancer | Upregulated      | 2.61 (1.51-4.51) | qRT-PCR           |
| Ji et al.        | Asian     | 2019 | tissue      | 35           | circSLC26A4      | 50            | Cervical cancer | Upregulated      | 2.53 (0.81-7.89) | qRT-PCR           |
| Ding et al.      | Asian     | 2019 | tissue      | 46           | Circ-ATP8A2      | 60            | Cervical cancer | Upregulated      | 2.32 (1.03-5.23) | qRT-PCR           |
| Song et al.      | Asian     | 2018 | serum       | 39           | hsa_circRNA_101996 | 80         | Cervical cancer | Upregulated      | 1.69 (0.43-6.68) | qRT-PCR           |
| Hong et al.      | Asian     | 2019 | tissue      | 48           | circCLK3         | 70            | Cervical cancer | Upregulated      | 4.09 (1.03-16.19)| qRT-PCR           |

CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, OS = overall survival, qRT-PCR = quantitative real-time polymerase chain reaction.

### Table 3
The expression and mechanisms of circRNAs in cervical cancer and ovarian cancer.

| Cancer type        | CircRNA signature | Expression | Function          | Mechanism                                                                 | Reference |
|--------------------|-------------------|------------|-------------------|---------------------------------------------------------------------------|-----------|
| Ovarian cancer     | circ0004390       | Upregulated| Cancer oncogene   | Regulates ovarian cancer proliferation by miR-198/MET axis                 | [19]      |
| Ovarian cancer     | circHIPK3         | Upregulated| Cancer oncogene   | NA                                                                         | [20]      |
| Ovarian cancer     | circ-ITCH         | Downregulated| Cancer suppressor gene | NA                                                                         | [18]      |
| Ovarian cancer     | circPIPSK1A       | Upregulated| Cancer oncogene   | NA                                                                         | [19]      |
| Ovarian cancer     | circPLEKH3M3      | Downregulated| Cancer suppressor gene | NA                                                                         | [20]      |
| Ovarian cancer     | circUBAP2         | Upregulated| Cancer oncogene   | Increases CDH2 expression by sponging miR-144                              | [13]      |
| Ovarian cancer     | circRNA_100395    | Downregulated| Cancer suppressor gene | Increases E-cadherin expression and N-cadherin and Snail expression via promoting p53 expression by sponging miR-1228 | [16]      |
| Ovarian cancer     | circ-ABCB10       | Upregulated| Cancer oncogene   | Inhibits miR-1271, miR-1252 and miR-203 expression                        | [14]      |
| Ovarian cancer     | hsa_circ_0051240  | Upregulated| Cancer oncogene   | Inhibits the miR-637/KLK4 axis                                            | [21]      |
| Ovarian cancer     | circLARP4         | Downregulated| Cancer suppressor gene | NA                                                                         | [22]      |
| Ovarian cancer     | circ-FAM53B       | Upregulated| Cancer oncogene   | NA                                                                         | [23]      |
| Cervical cancer    | circ_0018289      | Upregulated| Cancer oncogene   | NA                                                                         | [24]      |
| Cervical cancer    | circSLC26A4       | Upregulated| Cancer oncogene   | NA                                                                         | [25]      |
| Cervical cancer    | circ-ATP8A2       | Upregulated| Cancer oncogene   | NA                                                                         | [26]      |
| Cervical cancer    | hsa_circRNA_101996| Upregulated| Cancer oncogene   | NA                                                                         | [27]      |
| Cervical cancer    | circCLK3          | Upregulated| Cancer oncogene   | NA                                                                         | [28]      |

N/A = not applicable.
Figure 2. (A) Forest plots for overall survival according to the type of Ovarian cancer tumor-suppressor circRNA. (B) Forest plots for overall survival according to the type of Ovarian cancer oncogenic circRNA. (C) Forest plots for overall survival according to the type of cervical cancer oncogenic circRNA.
Figure 3. Forest plot of sensitivity and specificity of circRNAs for the diagnosis of Ovarian cancer.

Figure 4. Forest plot of sensitivity and specificity of circRNAs for the diagnosis of Cervical cancer.
3.5. Diagnosis analysis of circRNA on ovarian and cervical cancer

3.5.1. Ovarian cancer studies. The outcomes of pooled SEN and SPE of ovarian cancer were shown in Figure 3. A fixed-effect model was applied due to the no significant heterogeneity between the groups. The summary estimates are as follows: SPE, 0.85 (95% CI 0.78–0.90); SEN, 0.84 (95% CI 0.77–0.90); besides, a summary receiver operator characteristic curve was carried out in Figure 5 and AUC was 0.89 (95% CI 0.86–0.92).

3.5.2. Cervical cancer studies. The outcomes of pooled SEN and SPE of cervical cancer were shown in Figure 4. A fixed-effect model was applied due to the no significant heterogeneity between the groups. The summary estimates are as follows: SPE, 0.89 (95% CI 0.82–0.93); SEN, 0.83 (95% CI 0.75–0.88); besides, a summary receiver operator characteristic curve was carried out in Figure 5 and AUC was 0.93 (95% CI 0.90–0.95).

3.6. Publication bias

Judged by a Deeks funnel plot, there was no evidence of publication bias (P = .13) in the diagnostic analysis (see Fig. 2, Supplemental Content, http://links.lww.com/MD/G414, which illustrates the publication bias judged by Deeks funnel plot for the diagnostic meta-analysis). Publication bias can be measured using Beggs funnel plot and Egger test. A Beggs funnel plot (Fig. 6A, P = .976) and an Egger test (Fig. 6B, P = .936), indicated that there was no clear publication bias in the analysis of the tumor-suppressor circRNAs in terms of OS. There was also no publication bias in the analysis of oncogenic circRNAs in the case of OS, as indicated by a Beggs funnel plot (Fig. 6C, P = .945) and an Egger test (Fig. 6D, P = .900). These outcomes indicated that circRNAs are likely to be a favorable diagnostic and prognostic biomarker.

4. Discussion

This is the first meta-analysis explored circRNA for the diagnosis and prognosis of ovarian and cervical cancer. In terms of its mechanism and expression level, we regarded circRNAs as tumor promoters or tumor suppressors. Our outcomes demonstrated that dysregulated expression of circRNAs had a different impact on ovarian and cervical cancer survival. High expression levels of oncogenic circRNAs were significantly associated with poor prognoses both in ovarian and cervical cancer. However, elevated expression levels of tumor-suppressor circRNAs were linked with favorable survival time in ovarian cancer. In addition, the diagnostic significance of circRNAs was investigated as well. The AUC value in ovarian cancer and cervical cancer is 0.89 and 0.93, respectively. This suggesting that circRNA will be a novel biomarker in diagnosis. Besides, there was no obvious heterogeneity and publication bias performed by a SEN analysis.

Previous studies discovered circRNA can affect tumorigenesis, metastasis, and rebuilding of the tumor microenvironment. Through the study of Li et al.\textsuperscript{[16]} overexpression of circ100395 can inhibit the proliferation, migration, and invasion of ovarian cancer cells by regulating the miR-1228/p53/EMT axis; at the same time, Cai et al.\textsuperscript{[40]} found that circ0000263 was significantly upregulated in cervical cancer cells and ultimately affected the expression of p53 gene. We found p53 gene was a common gene in the development of ovarian cancer and cervical cancer. According, we inferred the potential use of circRNAs to regulated p53 gene might as therapeutic targets for the treatment of ovarian and cervical cancer. Several previous meta-analyses\textsuperscript{[41–42]} reported circRNA has important diagnostic and prognostic value in tumor. Huang et al.\textsuperscript{[43]} have summarized that circRNAs may act as important biomarkers for diagnosis and prognosis in diverse cancers by meta-analysis. There are few studies on ovarian and cervical cancer included in previous study. In our research, 22 studies involving 2059 patients with ovarian or cervical cancer were included, which markedly increased the statistical power and made the pooled results more credible. Additionally, the functions and mechanisms of circRNA in both cancers have been clarified.

Despite the promising data, there are some limitations to our study. First, the samples were all taken from cancerous tissues, and the diagnostic value of plasma samples was higher. More plasma samples are needed for further study. Second, all the patients in our study were selected from an Asian population, so the results may be biased. Third, the sample size in this study was small, so a larger clinical study is needed. Finally, some articles did not directly provide the survival data, so we had to estimate the HRs from Kaplan-Meier curves by the method of Parmar et al.\textsuperscript{[32]}
5. Conclusions

CircRNAs have the prospect of becoming a promising biomarker for diagnosis and prognosis of ovarian and cervical cancer. Accordingly, circRNAs might be novel indicators and targets of therapy for ovarian and cervical cancer.

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All authors have read and approved the manuscript.
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References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7–34.
[2] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
[3] Torre LA, Trabert B, DeSantis CE, et al. Ovarian cancer statistics, 2018. CA Cancer J Clin ;1; 2018;68:284–96.
[4] GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11. [accessed on 12 August 2019]; Available online: http://globocan.iarc.fr.
[5] Hosseini ES, Meryet-Figuere M, Salzalipoor H, Kashani HH, Nikzad H, Asemi Z. Dysregulated expression of long noncoding RNAs in gynecologic cancers. Mol Cancer 2017;16:107.
[6] Huang J, Zhou Q, Li Y. Circular RNAs in gynecological disease: promising biomarkers and diagnostic targets. Biosci Rep 2019;39.
[7] Memczak S, Jens M, Elefsinioti A, et al. Circular RNAs are a large class of animal RNAs with regulatory potency. Nature 2013;495:333–8.
[8] Salzman J, Gawad C, Wang PL, Lacayo N, Brown PO. Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. PLoS One 2012;7:e30733.
[9] Peina Shi. The emerging role of circular RNAs in gastric cancer. Am J Cancer Res 2018;8:1919–32.
[10] Zhao Z, Li X, Jia D, Hao P, Rao L, Li M. Hsa_circ_0054633 in peripheral blood can be used as a diagnostic biomarker for pre-diabetes and type 2 diabetes mellitus. Acta Diabetol 2017;54:237–45.
[11] Lu D, Xu A-D. Mini review: circular rnas as potential clinical biomarkers for disorders in the central nervous system. Front Genet 2016;7:53.
[12] Fan X, Weng X, Zhao Y, Chen W, Gan T, Xu D. Circular RNAs in cardiovascular disease: an overview. Biomed Res Int 2017;2017:5135781.
[13] Sheng M, Wei N, Yang H, Yan M, Zhao Q-X, Jing L-J. CircRNA UBAP2 promotes tumor proliferation and invasion in ovarian cancer. Cancer Biomark 2019;26:151–61.
[14] Ji F, Du R, Chen T, et al. Circular RNA circSLC26A4 Accelerates Cervical Cancer Progression via miR-1287-5p/HOXA7 Axis. Mol Ther Nucleic acids 2019;18:5135781.
[15] Sun Y, Li X, Chen A, et al. CircPIP5K1A serves as a competitive endogenous RNA to target EGFR by sponging miR-433 in cervical cancer. Int J Clin Exp Pathol 2017;10:950.
[16] Zhang M, Xia B, Xu Y, Zhang Y, Xu J, Lou G. Circular RNA (hsa_circ_0051240) promotes cell proliferation, migration and invasion in ovarian cancer through miR-637/KLK4 axis. Artif Cells Nanomed Biotechnol 2019;47:1224–33.
[17] Lu X, Lin S, Mo Z, et al. circRNA_100395 inhibits cell proliferation and metastasis in ovarian cancer via regulating miR-1228/p53/epithelial-mesenchymal transition (EMT) axis. J Cancer 2020;11:599–609.
[18] Luo L, Gao Y, Sun X. CircITCH correlates with small tumor size, decreased FIGO stage and prolonged overall survival, and it inhibits cells proliferation while promotes cells apoptosis in epithelial ovarian cancer. Cancer Biomark 2018;23:305–13.
[19] Sun Y, Li X, Chen A, et al. CircPPI5K1A serves as a competitive endogenous RNA contributing to ovarian cancer progression via regulation of miR-661/IGFBP5 signaling. J Cell Biochem 2019;120:19406–14.
[20] Hu Y, Zhu Y, Zhang W, Lang J, Ning L. Utility of plasma circBNC2 as a potential biomarker in cervical cancer patients: the clinical application of circular RNAs. J Clin Lab Anal 2020;e23292.
[21] Pei C, Wang H, Shi C, Zhang C, Wang M. CircRNA hsa_circ_0013958 may contribute to the development of ovarian cancer by affecting epithelial-mesenchymal transition and apoptotic signaling pathways. J Clin Laparosc Oncol 2020;526:14.
[22] Wang Y, Huang L, Li D, et al. Hsa_circ_0101996 combined with miR-615-5p and miR-6753-5p. Mol Ther Nucleic acids 2019;18:5135781.
[23] Huang X, Zhang W, Shao Z. Prognostic and diagnostic significance of circular RNAs in lung cancer. J Cell Physiol 2019;234:11391–400.
[24] Huang X, Zhang W, Shao Z. Prognostic and diagnostic significance of circRNAs expression in lung cancer. J Cell Physiol 2019;234:18459–65.
[25] Wang Y, Yang W, Zhang Z, Shao Z. Dysregulated circRNAs serve as prognostic and diagnostic markers in osteosarcoma by sponging miR-133b to regulate the downstream signaling pathway. J Cell Biochem 2020;121:1834–41.