Bioinformatics prediction and analysis of hub genes and pathways of three types of gynecological cancer

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Abstract. Cervical, endometrial and vulvar cancer are three common types of gynecological tumor that threaten the health of females worldwide. Since their underlying mechanisms and associations remain unclear, a comprehensive and systematic bioinformatics analysis is required. The present study downloaded GSE63678 from the GEO database and then performed functional enrichment analyses, including gene ontology and pathway analysis. To further investigate the molecular mechanisms underlying the three types of gynecological cancer, protein-protein interaction (PPI) analysis was performed. A biological network was generated with the guidance of the Kyoto Encyclopedia of Genes and Genomes database and was presented in Cytoscape. A total of 1,219 DEGs were identified for the three types of cancer, and 25 hub genes were revealed. Pathway analysis and the PPI network indicated that four main types of pathway participate in the mechanism of gynecological cancer, including viral infections and cancer formation, tumorigenesis and development, signal transduction, and endocrinology and metabolism. A preliminary gynecological cancer biological network was constructed. Notably, following all analysis, the phosphoinositide 3-kinase (PI3K)/Akt pathway was identified as a potential biomarker pathway. Seven pivotal hub genes (CCNA2, CDK1, CCND1, FGF2, IGF1, BCL2 and VEGFA) of the three gynecological cancer types were proposed. The seven hub genes may serve as targets in gynecological cancer for prevention and early intervention. The PI3K/Akt pathway was identified as a critical biomarker of the three types of gynecological cancer, which may serve a role in the pathogenesis. In summary, the present study provided evidence that could support the treatment of gynecologic tumors in the future.

Introduction

A gynecological tumor is a type of malignant tumor that occurs in the female reproductive system and seriously threatens the life of the patient. Among the types of gynecological tumor, cervical cancer (CC), endometrial carcinoma (EC) and vulvar carcinoma (VC) are the top three most common tumors of the female genital system, besides ovarian cancer (1). Despite an overall decline in the incidence and mortality rates due to increased understanding of the disease, gynecological cancer remains a significant health care burden worldwide (1). Early detection and treatment are essential for improving patient outcomes; however, these require improved understanding of the molecular pathology of the disease, in addition to identification of appropriate biomarkers and drug targets. Previous studies have demonstrated that the occurrence of CC is closely associated with human papillomavirus (HPV) infection (2-4). VC can be separated into two types, including one type that more frequently occurs in young females. This type involves the progression of a vulvar intraepithelial neoplasia caused by HPV infection, particularly HPV 16 and 18 (5). Based on pathogenetic perspectives, EC is also classified into two groups according to estrogen dependence (6). Although there have been a number of previous etiology studies, the exact pathogenesis of these three types of cancer remains unclear.

There are certain pathological and etiological associations between CC and VC, as both are squamous cell cancers and both are associated with HPV infection (2,5). Unlike CC and VC, EC is associated with sex hormones, which is similar to common invasive tumors in females, including breast and ovarian cancer (6). In addition, clinical diagnoses of these three cancer types rely predominantly on pathology (7). Precise biomarkers in early stages of CC, EC and VC remain unknown.

It is understood that cervical, endometrial and vulvar tissues all originate from the same embryological origin, the parimesonephric ducts, which give rise to the whole female reproductive tract and develop into different organs, following complex regulatory process (8). For this reason, although there a number of differences between CC, EC and VC, it has been hypothesized that these three types of gynecological tumor share a similar mechanism and certain specific marker molecules may be common to their tumorigenesis
betweenness scores higher than the mean, as calculated by the Cytoscape plugin Centscape, were considered hub nodes.

**GO analysis of the hub genes.** WEB-based Gene SeT AnaLysis Toolkit (http://www.webgestalt.org/; revision 2017) is a popular software tool for functional enrichment analysis, which covers seven biological contexts, including GO (14). Therefore, this software was used in the present study for GO enrichment analysis. The false discovery rate (FDR) was set at <0.05 to conduct the GO analysis of the DEGs.

**Pathway enrichment analysis of the hub genes.** The hub genes were uploaded to ToppGene (https://toppgene.cchmc.org/) for pathway enrichment analysis. The two frequently used databases, Kyoto Encyclopedia of Gene and Genomes (KEGG; www.genome.jp/kegg) and Biocarta (www.biocarta.com), were used to perform this analysis (15). The FDR was set at <0.05.

**Pathway crosstalk analysis.** The enriched pathways were recruited for further crosstalk analysis to investigate the associations between them. As described previously (15), to measure the association between two pathways, Jaccard coefficient (JC)=A∩B/A∪B and overlap coefficient (OC)=A∩B/min(|A|,|B|) were adopted, where A and B are the gene items contained in the two pathways, min is the minimum, ∩ is the intersection of A and B, and ∪ is the union of A and B. Since limited biological information was available, pathways containing <3 genes were excluded. Similarly, the pathway pairs with <2 overlapping genes were removed. Subsequently, the pathway network was presented with Cytoscape according to the JC and OC value of each selected pair (16), and the MCODE plug-in (17) (version 1.4.2; apps.cytoscape.org/apps/MCODE) for Cytoscape was used to find clusters and highly interconnected regions in any network was used to analyze the clusters.

**Gene-pathway network analysis.** To further investigate the developmental mechanisms of CC, EC and VC, the hub genes were mapped into a crosstalk network. By analyzing the interactions between the genes and pathways with KEGG and Biocarta, the connected nodes were linked with arrows. The gene-pathway network was constructed and visualized in Cytoscape. The degree was calculated and nodes with a degree greater than the mean degree of all nodes were selected to constitute a sub network.

**Results**

**Identification of DEGs.** Following screening with the criteria of P<0.05 and fold-change >2, a total of 1,219 DEGs were identified. In the CC group 138 DEGs were revealed, including 87 upregulated genes. In addition, 479 DEGs were identified in the EC group, including 272 upregulated genes. Finally, 734 DEGs, including 172 upregulated genes, were revealed in the VC group. As demonstrated in Fig. 2A, 84, 378 and 630 DEGs were exclusively identified in CC, EC and VC groups, respectively. However, 23 DEGs were present in both the CC and EC group, 73 DEGs were identified in both the EC and VC groups, and 26 DEGs were revealed in both the CC and VC groups. Furthermore, five mutual genes, including signal sequence...
receptor subunit 1 (SSR1), flap structure-specific endonuclease 1 (FEN1), cyclin A2 (CCNA2), signal transducer and activator of transcription 1 (STAT1) and C-X-C motif chemokine ligand 12 (CXCL12), were identified in all three groups. Hub genes and PPI network. Following calculation by Centiscape, the mean values of degree, closeness and betweenness were 12.64080, 3.73x10^{-4} and 2081.81034, respectively. Additionally, 25 hub genes were identified, including six downregulated genes and 19 upregulated genes (Table I). Three histone cluster family members were revealed as hub genes, including histone H2B type 1-H (HIST1H2BH), histone cluster 1 H2B family member D (HIST1H2BD) and histone cluster 1 H2B family member K (HIST1H2BK), and the five hub genes were cell cycle regulatory proteins, including CCNA2, cyclin B1 (CCNB1), cyclin D1 (CCND1), aurora kinase A (AURKA) and cell division cycle 20 (CDC20). Furthermore certain genes associated with tumor progression were identified, including vascular endothelial growth factor A (VEGFA), FYN proto-oncogene, Src family tyrosine kinase (FYN), baculoviral IAP repeat containing 5 (BIRC5) and the apoptosis regulator B-cell lymphoma 2 (BCL2).

Figure 1. Flowchart of the study. CC, cervical cancer; EC, endometrial cancer; VC, vulvar cancer, PPI, protein-protein interaction.
The PPI network of the 25 hub genes with 25 nodes and 114 edges is presented in Fig. 2B. The top five genes with the highest degrees were CDK1, CCNB1, CDC20, CCNA2 and AURKA. All five of these genes are associated with cell cycle regulation, which indicates that cell cycle dysfunction serves an important role in the development of gynecological tumors.

**GO enrichment analysis.** A total of 25 DEGs were used to perform GO enrichment analysis (Fig. 2C). For cellular component terms, 22 out of the 25 genes were revealed to be located in the ‘nucleus’ and approximately 80% were identified to participate in the ‘macromolecular complex’ (19 genes) and ‘membrane-enclosed lumen’ (18 genes). In the biological process category, the DEGs were associated with ‘cellular component organization’ (21 genes) and ‘response to stimulus’ (21 genes). In the molecular function category all 25 DEGs were associated with ‘protein binding’ (25 genes).

**Pathway enrichment analysis of the hub genes.** By uploading the 25 genes into ToppGene, 86 significant pathways were identified. The biological processes involved in these pathways can be divided into the following five main categories: i) viral infections and cancer formation, including ‘viral carcinogenesis’ and ‘hepatitis B’, ii) tumorigenesis and development, including ‘colorectal cancer’ and ‘proteoglycans in cancer’, iii) signal transduction, including ‘PI3K-Akt signaling pathway’ and ‘AMPK signaling pathway’, iv) endocrinology and metabolism, including ‘AGE-RAGE signaling pathway in diabetic complications’ and ‘endocrine resistance’, and v) others, including ‘genes encoding secreted soluble factors’ and ‘NFAT and hypertrophy of the heart (transcription in the broken heart)’. In addition, 19 pathways were identified to be downregulated and 17 pathways were revealed to be upregulated (Table II).

**Pathway crosstalk analysis.** To further investigate how the identified pathways interact with each other, a pathway
Crosstalk analysis was conducted among the pathways that met the criteria. The approach was based on the assumption that two pathways can be considered to be associated if they share a proportion of genes (18). A total of 45 pathways contained more than two hub genes, of which 41 pathways met the criterion for crosstalk analysis.

The network of crosstalk, which includes these 41 pathways, is presented in Fig. 3A. The thickness of edge connecting two nodes represents the strength of the association between them, which was measured by the mean value of OC and JC. Using MCODE, two major clusters were identified from the whole network. The simple cluster involves three pathways associated with cell cycle, including 'Cell cycle', 'Oocyte meiosis' and 'Cyclins and Cell Cycle Regulation'. The complicated cluster containing a total of 32 nodes and 376 edges is presented in Fig. 3B. The five aforementioned types of pathways were interconnected to form the complex network, which indicates the complexity of the pathogenesis of CC, EC and VC.

Gene-pathway network construction of DEGs. By mapping the hub genes into the complicated sub-network according to the KEGG and Biocarta databases, a potential gene-pathway network was constructed to verify the associations between the candidate pathways and genes (Fig. 4). This network included 37 important pathways and 18 hub genes, including CCND1 presented in the middle with direct or indirect associations with all other genes. As the only overlapping gene of all three groups, CCNA2 possessed complicated connections with 'viral carcinogenesis', 'hepatitis B', 'cell cycle' and six other pathways. In addition, insulin-like growth factor-1 (IGF1), fibroblast growth factor 2 (FGF2) and CCND1 were located close to the middle of the gene-pathway network.

Sub gene-pathway network of DEGs. To screen the key factors, including genes and pathways, in the gene-pathway network, the degrees of all nodes were calculated and nodes with a degree greater than the mean degree of all nodes were selected (Fig. 5). Seven genes (CCNA2, CDK1, CCND1, BCL2, IGF1, FGF2 and VEGFA) and six pathways ('Viral carcinogenesis', 'Hepatitis B', 'Focal adhesion', 'Pathways in cancer', 'PI3K-Akt signaling pathway' and 'Proteoglycans in cancer') were selected. Since these gene and pathways had more connections with other nodes, they were considered to more likely serve a role in CC, EC and VS.

Table I. Topological parameters of the hub genes.

| Gene    | Degree | Betweeness   | Closeness | Group | Regulation |
|---------|--------|--------------|-----------|-------|------------|
| Mean    | 13     | 2081.81034   | 3.73×10^-4|       |            |
| CDK1    | 115    | 20448.4838   | 5.21×10^-4| CC/EC | Up         |
| CCNB1   | 100    | 16335.9142   | 5.23×10^-4| CC/EC | Up         |
| CDC20   | 92     | 8148.54809   | 4.76×10^-4| EC    | Up         |
| CCNA2   | 91     | 8126.90458   | 4.89×10^-4| CC/EC/VC | Up |
| AURKA   | 90     | 9181.94344   | 4.76×10^-4| EC/VC | Up         |
| TOP2A   | 87     | 21409.6376   | 5.15×10^-4| EC/VC | Up         |
| UBE2C   | 82     | 14916.6491   | 4.82×10^-4| EC/VC | Up         |
| BIRC5   | 80     | 16279.0157   | 5.13×10^-4| EC/VC | Up         |
| PCNA    | 62     | 26080.2036   | 5.25×10^-4| CC/EC | Up         |
| VEGFA   | 56     | 32712.0335   | 5.43×10^-4| VC    | Up         |
| PIK3R1  | 46     | 24576.8505   | 4.91×10^-4| VC    | Down       |
| HIST1H2BK| 43    | 8689.20717   | 4.70×10^-4| CC/VC | Up         |
| HIST1H2BD| 43    | 8689.20717   | 4.70×10^-4| VC    | Up         |
| HIST1H2BH| 42    | 8291.98846   | 4.70×10^-4| VC    | Up         |
| ACACB   | 41     | 40853.547    | 4.98×10^-4| VC    | Down       |
| CXCL8   | 40     | 28927.396    | 5.16×10^-4| VC    | Up         |
| H2AFZ   | 39     | 8793.56814   | 4.67×10^-4| CC    | Up         |
| IGF1    | 38     | 16278.2011   | 5.07×10^-4| CC/VC | Down       |
| ACLY    | 37     | 34157.4527   | 4.81×10^-4| EC    | Up         |
| CCND1   | 36     | 28548.907    | 5.39×10^-4| EC    | Up         |
| GAPDH   | 33     | 41598.1258   | 5.39×10^-4| EC    | Up         |
| PPP2R5C | 32     | 10238.8057   | 4.75×10^-4| CC    | Up         |
| FYN     | 32     | 17254.3572   | 5.22×10^-4| CC/VC | Down       |
| FGF2    | 32     | 19465.3169   | 5.20×10^-4| EC    | Down       |
| BCL2    | 32     | 17923.6004   | 4.86×10^-4| VC    | Down       |

CC, cervical cancer; EC, endometrial cancer; VC, vulvar cancer.
Table II. Pathways enriched in three types of gynecological cancer.

| Pathway                                           | Regulation | P-value   | Genes in the pathway                     |
|---------------------------------------------------|------------|-----------|------------------------------------------|
| Viral carcinogenesis                              | -          | 3.43x10^-9| HIST1H2BD, CCND1, CDK1, HIST1H2BH, CDC20, PIK3R1, HIST1H2BK, CCNA2 |
| Hepatitis B                                       | -          | 9.66x10^-9| BIRC5, CCND1, BCL2, PIK3R1, PCNA, CXCL8, CCNA2 |
| AMPK signaling pathway                            | -          | 1.13x10^-7| CCND1, PPP2R5C, IGFl, ACACB, PIK3R1, CCNA2 |
| Oocyte meiosis                                    | -          | 1.31x10^-7| AURKA, PPP2R5C, IGFl, CDK1, CDC20, CCNB1 |
| Cell cycle                                        | Up         | 1.31x10^-7| CCND1, CDK1, CDC20, PCNA, CCNA2, CCNB1  |
| EGFR tyrosine kinase inhibitor resistance         | -          | 4.35x10^-7| FGF2, BCL2, IGFl, PIK3R1, VEGFA          |
| Pathways in cancer                                | -          | 6.44x10^-7| FGF2, BIRC5, CCND1, BCL2, IGFl, PIK3R1, CXCL8, VEGFA |
| Progesterone-mediated oocyte maturation           | -          | 1.15x10^-6| IGFl, CDK1, PIK3R1, CCNA2, CCNB1         |
| AGE-RAGE signaling pathway in diabetic complications| -          | 1.35x10^-6| CCND1, BCL2, PIK3R1, CXCL8, VEGFA      |
| HIF-1 signaling pathway                           | -          | 1.49x10^-6| BCL2, IGFl, GAPDH, PIK3R1, VEGFA       |
| Focal adhesion                                    | -          | 2.13x10^-6| CCND1, BCL2, IGFl, FYN, PIK3R1, VEGFA  |
| PI3K-Akt signaling pathway                        | -          | 3.48x10^-6| FGF2, CCND1, BCL2, PPP2R5C, IGFl, PIK3R1, VEGFA |
| p53 Signaling Pathway                             | -          | 3.94x10^-6| CCND1, BCL2, PCNA                      |
| IL-7 Signal Transduction                          | Down       | 4.77x10^-6| BCL2, FYN, PIK3R1                      |
| Colorectal cancer                                 | -          | 5.72x10^-6| BIRC5, CCND1, BCL2, PIK3R1             |
| p53 signaling pathway                             | -          | 1.00x10^-5| CCND1, IGFl, CDK1, CCNB1               |
| Melanoma                                          | -          | 1.00x10^-5| FGF2, CCND1, IGFl, PIK3R1               |
| Cyclins and Cell Cycle Regulation                 | Up         | 1.23x10^-5| CCND1, CDK1, CCNB1                    |
| Platinum drug resistance                          | -          | 1.25x10^-5| BIRC5, BCL2, PIK3R1, TOP2A             |
| Regulation of BAD phosphorylation                 | Down       | 1.80x10^-5| BCL2, IGFl, PIK3R1                     |
| Prostate cancer                                   | -          | 2.52x10^-5| CCND1, BCL2, IGFl, PIK3R1              |
| Endocrine resistance                              | -          | 3.71x10^-5| CCND1, BCL2, IGFl, PIK3R1              |
| Proteoglycans in cancer                           | -          | 4.47x10^-5| FGF2, CCND1, IGFl, PIK3R1, VEGFA      |
| Bladder cancer                                    | Up         | 7.25x10^-5| CCND1, CXCL8, VEGFA                    |
| Sphingolipid signaling pathway                    | -          | 8.32x10^-5| BCL2, PPP2R5C, FYN, PIK3R1             |
| FoxO signaling pathway                            | -          | 1.29x10^-4| CCND1, IGFl, PIK3R1, CCNB1             |
| Systemic lupus erythematosus                      | Up         | 1.32x10^-4| H2AFZ, HIST1H2BD, HIST1H2BH, HIST1H2BK|
| NFAT and Hypertrophy of the heart                 | Down       | 1.66x10^-4| FGF2, IGFl, PIK3R1                     |
| (Transcription in the broken heart)               |            |           |                                          |
| Breast cancer                                     | -          | 1.80x10^-4| FGF2, CCND1, IGFl, PIK3R1              |
| Activation of Src by Protein-tyrosine phosphatase alpha| Up   | 2.11x10^-4| CDK1, CCNB1                           |
| Sonic Hedgehog (SHH) Receptor Ptc1 Regulates cell cycle | Up   | 2.11x10^-4| CDK1, CCNB1                           |
| AKAP95 role in mitosis and chromosome dynamics    | Up         | 2.52x10^-4| CDK1, CCNB1                           |
| Glioma                                            | -          | 2.75x10^-4| CCND1, IGFl, PIK3R1                   |
| Pancreatic cancer                                 | -          | 2.75x10^-4| CCND1, PIK3R1, VEGFA                  |
| Expression of cyclins regulates progression through the cell cycle by activating cyclin-dependent kinases. | Up         | 2.98x10^-4| CCND1, CCNA2                          |
| The IGF-1 Receptor and Longevity                  | Down       | 4.00x10^-4| IGFl, PIK3R1                          |
| Alcoholism                                         | Up         | 4.22x10^-4| H2AFZ, HIST1H2BD, HIST1H2BH, HIST1H2BK|
| B Cell Survival Pathway                           | -          | 4.57x10^-4| BIRC5, PIK3R1                         |
| Small cell lung cancer                            | -          | 6.12x10^-4| CCND1, BCL2, PIK3R1                   |
| Stathmin and breast cancer resistance to antimicrotubule agents | Up | 6.48x10^-4| CDK1, CCNB1                          |
Table II. Continued.

| Pathway                                           | Regulation | P-value     | Genes in the pathway |
|---------------------------------------------------|------------|-------------|----------------------|
| Epstein-Barr virus infection                      | -          | 6.64x10^{-4}| BCL2, CDK1, PIK3R1, CCNA2 |
| Skeletal muscle hypertrophy is regulated via       | Down       | 7.19x10^{-4}| IGFl, PIK3R1         |
| AKT/mTOR pathway                                  |            |             |                      |
| Rap1 signaling pathway                            | -          | 7.54x10^{-4}| FGF2, IGFl, PIK3R1, VEGFA  |
| IGF-1 Signaling Pathway                           | Down       | 7.94x10^{-4}| IGFl, PIK3R1         |
| Ras signaling pathway                             | -          | 1.01x10^{-3}| FGF2, IGFl, PIK3R1, VEGFA  |
| Erk and PI-3 Kinase Are Necessary for Collagen Binding in Corneal Epithelia | Down | 1.04x10^{-3}| FYN, PIK3R1         |
| Cell Cycle: G2/M Checkpoint                       | Up         | 1.04x10^{-3}| CDK1, CCNB1         |
| Influence of Ras and Rho proteins on G1 to S Transition | -       | 1.22x10^{-3}| CCND1, PIK3R1       |
| Genes related to IL4 receptor signaling in B lymphocytes | Down     | 1.32x10^{-3}| BCL2, PIK3R1       |
| Inactivation of Gsk3 by AKT causes accumulation of b-catenin in Alveolar Macrophages | Up     | 1.32x10^{-3}| CCND1, PIK3R1       |
| Cholinergic synapse                                | Down       | 1.41x10^{-3}| BCL2, FYN, PIK3R1   |
| Cell Cycle: G1/S Check Point                      | Up         | 1.42x10^{-3}| CCND1, CDK1         |
| VEGF, Hypoxia, and Angiogenesis                   | -          | 1.52x10^{-3}| PIK3R1, VEGFA       |
| HTLV-I infection                                  | -          | 1.57x10^{-3}| CCND1, CDC20, PIK3R1, PCNA |
| Control of skeletal myogenesis by HDAC and calcium/calmodulin-dependent kinase (CaMK) | Down | 1.63x10^{-3}| IGFl, PIK3R1       |
| Apoptosis-multiple species                        | -          | 1.97x10^{-3}| BIRC5, BCL2         |
| How Progesterone Initiates Oocyte Membrane        | Up         | 2.09x10^{-3}| CDK1, CCNB1         |
| Measles                                           | -          | 2.36x10^{-3}| CCND1, FYN, PIK3R1  |
| Aldosterone-regulated sodium reabsorption         | Down       | 2.47x10^{-3}| IGFl, PIK3R1        |
| Apoptosis                                         | -          | 2.56x10^{-3}| BIRC5, BCL2, PIK3R1 |
| IL-2 Receptor Beta Chain in T cell Activation     | Down       | 2.60x10^{-3}| BCL2, PIK3R1        |
| Signaling pathways regulating pluripotency of stem cells | Down   | 2.62x10^{-3}| FGF2, IGFl, PIK3R1  |
| Fluid shear stress and atherosclerosis            | -          | 2.78x10^{-3}| BCL2, PIK3R1, VEGFA |
| Phospholipase D signaling pathway                 | -          | 3.01x10^{-3}| FYN, PIK3R1, CXCL8  |
| Jak-STAT signaling pathway                        | -          | 3.63x10^{-3}| CCND1, BCL2, PIK3R1 |
| Members of the BCR signaling pathway              | Down       | 3.80x10^{-3}| BCL2, PIK3R1        |
| Hedgehog signaling pathway                        | -          | 3.96x10^{-3}| CCND1, BCL2         |
| T Cell Receptor Signaling Pathway                 | Down       | 3.96x10^{-3}| FYN, PIK3R1         |
| Endometrial cancer                                | -          | 4.47x10^{-3}| CCND1, PIK3R1       |
| Genes encoding secreted soluble factors           | -          | 4.58x10^{-3}| FGF2, IGFl, CXCL8, VEGFA |
| Acute myeloid leukemia                            | -          | 5.39x10^{-3}| CCND1, PIK3R1       |
| Non-small cell lung cancer                        | -          | 5.97x10^{-3}| CCND1, PIK3R1       |
| VEGF signaling pathway                            | -          | 6.18x10^{-3}| PIK3R1, VEGFA       |
| Viral myocarditis                                 | -          | 6.18x10^{-3}| CCND1, FYN          |
| Longevity regulating pathway-multiple species     | Down       | 6.80x10^{-3}| IGFl, PIK3R1        |
| Renal cell carcinoma                              | -          | 7.45x10^{-3}| PIK3R1, VEGFA       |
| Fc epsilon RI signaling pathway                   | -          | 8.13x10^{-3}| FYN, PIK3R1         |
| Prolactin signaling pathway                       | -          | 8.60x10^{-3}| CCND1, PIK3R1       |
| Chronic myeloid leukemia                          | -          | 8.84x10^{-3}| CCND1, PIK3R1       |
| Longevity regulating pathway                      | -          | 1.36x10^{-2}| IGFl, PIK3R1        |
| Genes related to Wnt-mediated signal transduction | Up         | 1.36x10^{-2}| CCND1, GAPDH        |
| Rheumatoid arthritis                              | Up         | 1.39x10^{-2}| CXCL8, VEGFA        |
| NF-kappa B signaling pathway                      | -          | 1.54x10^{-2}| BCL2, CXCL8         |
| Amoebiasis                                        | -          | 1.57x10^{-2}| PIK3R1, CXCL8       |
| Cdc25 activates the cdc2/cyclin B complex to induce the G2/M transition. | Up | 1.60x10^{-2}| CDK1              |
| Inflammatory mediator regulation of TRP channels   | Down       | 1.60x10^{-2}| IGFl, PIK3R1        |
In the past few decades, gynecological cancer research has developed rapidly, particularly regarding the recognition of etiological factors. Although a number of studies have investigated CC, EC and VC separately, few studies have focused on these three types of cancer in combination. The aim of the present study was to perform a systematic and comprehensive analysis to investigate the pathogenesis of CC, EC and VC and make a preliminary assessment of the associations between these three cancer types.

By performing an analysis of microarray data, 1,219 DEGs were identified, including 138 in CC, 479 in EC and 734 in VC. Five DEGs were revealed in all three cancer types, which suggests these genes may participate in a number of important biological processes in gynecological cancer and may serve as crucial biomarkers following further research. Together with the 25 hub genes identified, these data may provide a direction for future research on gynecological cancer and assist with the identification of clinical biological targets.

Pathway enrichment analysis indicated that 86 pathways are closely associated with the 25 hub genes. In particular, it
was identified that viral infection and carcinogenesis pathways were significantly enriched, including ‘viral carcinogenesis’, ‘HTLV-1 infection’ and ‘hepatitis B’, which supports the association of virus with the three gynecological cancer types, particularly CC. Furthermore, cancer-association pathways, including ‘pathways in cancer’ and ‘proteoglycans in cancer’ were revealed to be associated with the biological process of the three malignant tumor types. Notably, multiple different types of human cancer, including melanoma, prostate cancer, bladder cancer, breast cancer and glioma, were also identified to be associated with the 25 hub genes. This indicates that gynecological cancer types may exhibit homologous mechanisms with tumor types of other systems.

With the gene-pathway sub-network model, seven critical hub genes and six important pathways of the three gynecological cancer types were identified. The hub genes with the highest degrees included CDK1, which was enriched in CC and VC. As reported, CDK1 is a member of the Ser/Thr protein kinase family and is encoded by cell division cycle gene 2 (cdc2) (19). In addition, CDK1 has been revealed to serve a role in numerous types of cancer, including EC (20), breast cancer (21) and ovarian cancer (22). Consistent with the present bioinformatics results, CDK1 has been demonstrated to serve a comprehensive role in mediating genetic networks involved in the progression of CC; therefore, it may be an important therapeutic target for improving prognosis (23). A study regarding ovarian cancer identified that CDK1 is associated with proliferation and can serve as a prognostic factor in epithelial ovarian cancer (22). In EC, the overexpression of CDK1 in endometrial carcinoma cells is closely associated with the occurrence of tumors, indicating a role in tumor progression (24). The CDK1 gene can contribute to the carcinogenesis of HPV (25), and CC and VC are associated with HPV infection; therefore, CDK1 may be an important molecule in the pathogenesis of gynecological tumors.

Another cell cycle regulatory gene, CCNA2, was revealed as a shared DEG of CC, EC and VC, and complicated connections were identified between it and other nodes. According to recent studies, CCNA2 belongs to the highly conserved cyclin family and is expressed in multiple tissues in the human body, including numerous types of cancer, which indicates it may serve a role in cancer transformation and progression (26,27). Gao et al (28) revealed that CCNA2 is a prognostic biomarker for estrogen receptor-positive breast cancer and is associated with Tamoxifen resistance. Combined with another biological analysis of EC that demonstrated CCNA2 is one of the top two upregulated nodes (29), the present study hypothesizes that CCNA2 serves a role as a biomarker in gynecological tumors (29). In addition, a study associated with ovarian cancer revealed a similar result, in which CCNA2 was upregulated in the chemo-resistant epithelial ovarian cancer (30). Therefore, it can be suggested that CCNA2 is a potential biomarker in gynecological cancer; however, this requires in vivo or in vitro experimental verification. CCND1 is an important positive regulator of the G1/S phase of the cell cycle and has been identified as a co-factor of HPV in the initiation of cervical carcinogenesis (31). Similar studies regarding EC and VC have also widely been reported (32-34).

BCL2 and IGF1 were revealed as the only two downregulated genes in the sub-network. BCL2 is an intracellular membrane protein that prevents apoptotic cell death and overexpression of BCL2 can block p53-mediated G1 arrest (35).
Kamaraddi et al (36) demonstrated that BCL2 expression is higher in malignant lesions compared with premalignant lesions, which differs from the current findings. It has been suggested that alterations of BCL2 expression are associated with early events in cervical tumorigenesis and a lower BCL2 expression level has also been demonstrated to be associated with an improved 5-year survival rate and prognosis (37). The significance of BCL2 in gynecological tumors requires further investigation. Furthermore, IGF1 is closely associated with the occurrence of numerous tumor types; however, its exact mechanism remains unclear. Iyer et al (38) identified that IGF-1 expression levels in advanced CC increase with chemotherapy and decline during follow-up (38). With a limited specificity in gynecologic tumors, IGF1 is of limited value in the early prediction of gynecological tumors; however it may serve a role in targeted treatment strategies, and the assessment and improvement of prognosis (39,40).

Angiogenesis serves an important role in tumor growth, development, progression and metastasis (41). As a pro-angiogenesis factor, VEGFA is involved in the proliferation, differentiation and migration of endothelial cells, and participates in the invasion and metastasis of numerous types of cancer (42). Chen et al (43) demonstrated that VEGFA may be a target for inhibiting angiogenesis in EC (42). Similarly, Hua and Tian (44) revealed that CCL4 can promote cell proliferation, invasion and migration of EC by targeting the VEGFA signal pathway (44). Combined with the present results, this indicates that VEGFA serves an important role in gynecological tumor invasion and metastasis.

FGF2 is a typical fibroblast growth factor that stimulates the growth of various cell types, from fibroblasts to tumor cells (45). In addition, FGF2 is a fundamental signaling molecule in tumor-induced angiogenesis (46). It has been demonstrated that FGF2 is mitogenic in various cell types and is associated with the regulation of tumor angiogenesis and metastasis (47). Certain studies regarding the receptor family of FGF2 have revealed that it is associated with the occurrence and development of CC, in addition to HPV16 infection (48,49). Aberrant FGF/FGF receptor signaling has been demonstrated in multiple types of tumor (50,51). The expression level of FGF2 has been revealed to be higher in EC compared with normal tissues, and the highest expression level was observed in tumors with dedifferentiation, myometrial invasion and advanced staging (52). Therefore, angiogenesis has an important impact in the pathogenesis of gynecological cancers.

‘PI3K-Akt signaling pathway’, ‘hepatitis B’, ‘pathways in cancer’, ‘focal adhesion’, ‘viral carcinogenesis’ and ‘proteoglycans in cancer’ were located in the sub-network, which indicates that these processes serve an important role in the pathogenesis of CC, EC and VC. It is understood that the PI3K/Akt signaling pathway serves a central role in cell growth and proliferation, and it has also been suggested that its deregulation is associated with cancer (53). Yung et al (54) demonstrated that the activation of AMPK could significantly inhibit CC cell growth. Similar studies regarding the PI3K/Akt pathway in EC have also been reported (55,56), and it has been considered as a therapeutic target (57). According to previous studies, the PI3K/Akt signaling pathway can serve as a therapeutic target in EC (57) and ovarian cancer (58,59), and can be mediated by molecules, including VEGFA (40). FGF2 has also been reported to serve an angiogenic role by the PI3K/Akt pathway (60). Furthermore, BCL2 is a major downstream mediator of the PI3K/Akt pathway and serves a pivotal role in tumor response (61,62). It has been reported that CCNA2 expression promotes the migration, invasion and metastasis of hepatocellular carcinoma and ovarian cancer cells via the PI3K/Akt signaling pathway (63). Therefore, this crucial pathway in cancer cells may be involved in the early developmental stages of formation and invasion. As indicated by the present results, the molecular mechanisms underlying CC, EC and VC are complicated, and further studies are required to fully understand their pathological mechanisms.

Similarly, Suman and Mishra (64) identified that the aurokinase pathway has a crucial function in the pathogenesis of five gynecological cancer types, including breast cancer, EC, CC, ovarian cancer and VC, by analyzing the common core genes from the GSE63678, GSE57297 and GSE26712 datasets. Furthermore, the present study identified seven genes (CCNA2, CDC1, CCND1, BCL2, IGF1, FGF2 and VEGFA) and six pathways (‘viral carcinogenesis’, ‘hepatitis B’, ‘focal adhesion’, ‘pathways in cancer’, ‘PI3K-Akt signaling pathway’ and ‘proteoglycans in cancer’) that may serve an important role in CC, EC and VC. A number of factors are involved in the progression of cancer; the present study focused on the factors associated with the female reproductive system. The results may provide comprehensive evidence that promotes the understanding of cancers of the female genital tract. While previous studies have focused on co-expressed DEGs (23,64), the present study aimed to establish a gene-pathway network based on the analysis of DEGs. Additionally, previous studies investigated genes co-expressed by the five cancer types (breast cancer, EC, CC, ovarian cancer and VC). However, the current study not only investigated the co-expressed DEGs of CC, EC and VC, but also examined the DEGs co-expressed by any combination of two of the cancer types. In summary, the current study focused on the genetic interactions between three types of tumor, which may make it more comprehensive compared with previous studies.

Notably, there are certain limitations to the present study. The sample number was relatively small, which to a certain extent reduces the credibility of gene enrichment. Subject to conditions, long-term assessments of the patients’ clinical conditions were not available. In addition, the literature regarding the pathways associated with CC, EC and VC, except for the PI3K/Akt pathway is limited; therefore, the present study lacked a solid foundation to adequately discuss the current results. Finally, certain genes that are associated with the pathogenesis of gynecological types of cancer may not have been statistically analyzed, possibly due to the exclusion criteria that was applied.

In conclusion, the pathogenesis of CC, EC and VC is complicated. By performing a comprehensive analysis, the present study revealed a library of DEGs in CC, EC and VC, and identified 25 hub genes. Subsequently, viral infection, tumorigenesis, inflammation and the endocrine system were revealed to be involved in the development of these three types of cancer. Finally, a molecular network of CC, EC and VC was constructed. Most notably, it was identified that the PI3K/Akt pathway serves an important role in the three types of gynecological cancer and seven hub genes (CCNA2, CDC1, CCND1, FGF2, IGF1, BCL2 and VEGFA) present in the sub-network.
may act as therapeutic targets, and assist with early diagnosis and prevention. The present study may support the elucidation of the underlying mechanisms in CC, EC and VC, which would promote early detection and the development of targeted therapy. Further investigations that aim to improve understanding of the mechanisms of these three cancer types will be vital for developing highly sensitive and multifactorial strategies for the prevention, diagnosis and treatment of CC, VC and EC.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors’ contributions

YL, YY and WZ conceived and designed the study. YY, WW, and KW analyzed the data. YL wrote the manuscript with contributions from all authors. All authors contributed to the interpretation of the data and writing the manuscript. The final version of the manuscript was reviewed and approved by all the authors.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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