Review Article

The Progression and Prospects of the Gene Expression Profiling in Ovarian Epithelial Cancer

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Abstract

Ovarian cancer is one of the most common cancers with a high mortality rate among females worldwide. The understanding of the pathogenesis of the disease is highly important to provide personalized therapy to the patients. Ovarian cancer is as heterogeneous as colon and breast cancer which makes it difficult to treat. The development of gene signature is the only hope in providing targeted therapy to improve the survival of ovarian cancer patients. Malignant epithelial carcinomas are the most common cancers of the ovary with different histological and molecular subtypes and clinical behavior. The development of precursor lesions of ovarian carcinoma in the tubes and endometrium has provided a new dimension to the origin of ovarian cancers. The clinical utility of various gene signatures may not be logical unless validated. Validated gene signatures can aid the clinician in deciding the appropriate line of treatment.

Keywords: Chemoresistance, gene signature, high-grade serous carcinoma, ovarian cancer, prognosis, validation

Introduction

Ovarian cancer is one of the most common cancers with a high mortality rate among females worldwide.[1,2] The incidence and mortality rate of ovarian cancer patients is increasing every year as the tumor is heterogeneous with complex pathogenesis and progression. This complexity has led to failure to effectively treat and prevent ovarian cancer.[3-5] Among ovarian cancer, malignant epithelial tumor constitutes around 95% and the other 5% is nonepithelial tumors. The high-grade serous carcinoma is the most common comprising around 70% of all ovarian cancers.[6,7] The advancement in the understanding of malignant epithelial tumor pathogenesis has led to Type I and Type II classification. The mucinous, low-grade serous, clear cell carcinomas are indolent with better survival chances, designated as Type I. The more aggressive tumors like high-grade serous, undifferentiated, and carcinosarcomas are designated as Type II.[8,9] A recent International Federation of Gynecology and Obstetrics (FIGO) staging system divides ovarian carcinoma into four stages with the integration of the fallopian tube and peritoneal involvement and recommends the institution of chemotherapy for high-grade tumor Stage Ic and Stage II–IV ovarian cancer.[10] The controversy persists regarding the benefits of chemotherapy as ovarian cancers are heterogeneous. The microarray gene signature analysis carried out on Stage I to Stage IV ovarian cancer has provided new prognostic indicators, risk stratification, and prediction of survival.[11] The gene expression profiling of ovarian cancer started as early as 2003, and large data sets are available to develop gene signatures. However, a prospective study is required to validate and translate the research data to clinical use.[12,13] The prognostic gene signature can bridge the gap between the average 5-year survival rate of early (90%) and advanced (10%–20%) ovarian cancer.[14,15] The early gene signature study was able to divide malignant epithelial

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tumors into lymphocyte and epithelial and stromal clusters depending on the characteristics of genes.[13] After a series of studies, systematic high-grade molecular subtypes have been described. The important validated four subtypes are C1 (mesenchymal), C2 (immune reactive), C4 (differentiated), and C5 (proliferative).[16,17] The large-scale genomic analysis classified the C5 proliferative group into stem-like A and stem-like B.[18] The molecular classification has led to better clinical correlation and prediction of disease-free survival in malignant epithelial ovarian cancer.[19-21] This present-day article is an overview of the advancement in gene profiling of ovarian cancer.

Discussion

The development of gene signatures for ovarian cancer has been quite challenging as the malignant cells and admixed stromal cells, as well as other cells, vary from tumor to tumor.[22] Based on morphological features, ovarian cancers are classified into epithelial and nonepithelial. The epithelial tumors are further classified into serous (low and high grade), mucinous, endometrioid, and clear cell carcinoma [Table 1].[23] The high-grade serous tumors frequently may have TP53, BRCA1/2, and PIK3CA with chromosomal instability mutations. The low-grade serous, mucinous, endometrioid, and clear cell carcinoma may have mutations in PTEN, KRAS, BRAF, CTNNB1, microsatellite instability, and β-catenin.[16,24,25]

The best approach for the molecular characterization of cancers is microarray-based gene expression profiling [Table 2]. Microarray technology is a powerful high-throughput platform for gene research.[26] It has been widely used to determine possible genetic or epigenetic alternations and identify biomarkers in various disorders.[27,28] As early as 2004, Spentzos *et al*. validated 115 genes associated with overall survival using Affymetrix assay in stage III and IV ovarian cancer. The oligonucleotide microarray was used to profile the tumor tissue of 68 ovarian cancer patients. The 115-gene signature, referred to as the Ovarian Cancer Prognostic Profile, was able to differentiate between patients with favorable and unfavorable overall survival independent of age, histological grade, FIGO stage, and debulking status. The Ovarian Cancer Prognostic profile was able to predict the probability of overall survival after receiving standard first-line platinum-based therapy.[29] Marquez *et al*., in 2005, using microarray analysis established that the gene expression of serous tumors is similar to the normal fallopian tubes, mucinous tumors resembled normal colonic mucosa, and endometrioid and clear cells are look-alike of normal endometrium.[30] In the same year, Berchuck *et al*., using Affymetrix U133A microarrays, analyzed the RNA of 65 serous ovarian cancers of stage I–IV. A 26-gene signature was used, of which myelin and lymphocyte (MAL) protein encoded by the MAL gene, heat shock protein 27, and lysophospholipase II were consistently upregulated in short-term survivors in comparison to long-term

Table 1: Histological type, incidence, immunophenotype, molecular alteration, and prognosis of malignant epithelial tumors

Histologic type	Incidence (%)	Immunophenotyping	Molecular alterations	Prognosis
High-grade serous carcinoma	70	CK7, p16, PAX8, WT1, and ER and PgR positivity	Somatic p53 mutation Genomic alteration in HRR pathway	HRR proficient tumor – worse prognosis HRR deficient tumor – better prognosis
Low-grade serous carcinoma	5	CK7, PAX8, WT1, and ER and PgR positivity	Activated mutations of upstream regulators of MAPK signal transduction pathway	KRAS mutation – unfavorable BRAF mutation – better prognosis
Endometrioid carcinoma	10	CK7, PAX8, and ER and PgR positivity	Mutations in PIK3CA, ARID1A, KRAS, and CTNNB1	CTNNB1 – good prognosis KRAS mutation – unfavorable
Mucinous carcinoma	3	CK7 positivity and variable positivity for CA19-9, CEA, CK20, and CDX2	KRAS and TP53 mutations, CDKN2A inactivation, and HER2/neu gene amplification	Unfavorable prognosis
Clear cell carcinoma	10	Napsin A and HNF1β positivity	PIK3CA-activating mutations, TP53 mutation, and MMR germline mutation	TP53 – adverse prognosis MMR deficient – favorable prognosis

HRR: Homologous recombination repair, PgR: Progesterone receptor, ER: Estrogen receptor

Table 2: Selected microarray studies that have identified prognostic gene expression profiles in epithelial ovarian cancer

Reference	Number of patients in the training set	Number of patients in the validation set	Microarray platforms	Findings
Berchuck *et al*. (2005)[31]	54	11	U133A (Affymetrix) Oligonucleotides	Expression model that distinguished survival <3 years versus >7 years
Yoshihara K (2010)[48]	87	87	Agilent Whole Human Genome Oligo Microarray	Evaluation of the risk of recurrence in patients with advanced-stage serous ovarian cancer
Fei *et al*. (2020)[49]	89	89	NCBI-GEO database	KIF11, CDC20, and TOP2A expressions are significantly related to the prognosis of SCA patients

NCBI-GEO: NCBI-gene expression omnibus, SCA: Ovarian serous Carcinoma

survivors of serous carcinoma. Apart from providing potential targets for therapy, the study was able to establish that the molecular alterations in early serous carcinoma and long-term survivors of advanced carcinoma were similar. However, comparison and validation of Berchuck *et al.*'s study with Spentzos could not be carried out as different microarray platforms were used.[31] Jazaeri *et al*. generated an 85-gene expression profile from 24 primary chemoresistant tumors and 21 primary chemosensitive tumors by cDNA-based microarrays and then compared with 15 postchemotherapy tumors. A distinct differential expression of all 85 genes was noted and concluded that by gene expression profiling, intrinsic and acquired drug resistance can be identified, and targeted therapy can be instituted in patients.[32] For the first time in 2008, Bonome *et al*. developed a 57-gene signature using Affymetrix Human U133A GeneChip oligonucleotide microarrays to predict the survival in suboptimally debulked tumors in stage III ovarian serous cancer and also recognized that the survival of the patient is closely related to alterations in pathways modulating cell proliferation, chromatin maintenance, secretion, apoptosis, motility, and chemoresistance.[33] In the following year, a retrospective study of advanced ovarian cancer led to the development of the 86-gene expression using the Netherlands National Cancer Institute oligonucleotide array which preserved independent prognostic significance in both univariate and multivariate analyses. The signaling pathways and transcription factors associated with ovarian cancer were also studied to aid in the development of targeted therapy. In 2019, Wang explained the role of laparoscopy in advanced ovarian epithelial carcinoma as it has high specificity in identifying the resectability and also explained about the peritoneal carcinoma index which assists in identifying the patients whether to proceed with laparotomy or not.[34] In 2018, Tantitamit and Lee did a study and recommended that laparoscopic surgery is the preferred option for early-stage ovarian epithelial malignancy with the precaution of tumor spillage/port site metastasis.[35] In 2020, Palakkan *et al*. studied the role of frozen section in ovarian neoplasms, which helps to decide further management, and proved that it has 93% accuracy.[36] Apart from gene expression, the study was able to validate the Kyoto Encyclopedia of Genes and Genomes pathway and a Transcriptional Regulatory Element Database factors associated with overall survival in advanced ovarian cancer.[37] In 2022, Zhou and Chenang studied the role of microRNA-133 in gynecological malignancies and found it to have tumor-inhibiting effects on ovarian cancers and promote cervical cancer growth.[38] In 2010, Konstantinopoulos *et al*. developed a BRCAness 60-gene profile using an Affymetrix array in 70 patients of stage I–IV sporadic ovarian epithelial cancer. The 60-gene profile was able to differentiate BRCA-like and non-BRCA-like tumor profiles. The BRCA-like tumor responsiveness to platinum and poly-ADP ribose polymerase inhibitor helped to predict the better survival group in sporadic cancers.[39] A large-scale genomic study of high-grade serous carcinoma by the Cancer Genome Atlas (TCGA) revealed the distinct and heterogeneous genetic mutations in serous carcinoma of the ovary. A 193-gene transcriptional signature was developed using Affymetrix and Agilent array, which helps to predict the overall survival of patients with advanced serous carcinoma. The most consistent and frequent was TP53 mutation, followed by BRCA1, BRCA2, BRCA1/2, RB1, NF1, FAT3, CSMD3, GABRA6, and CDK12 mutations.[17] A small gene panel of seven genes was derived from 94 genes that could predict disease-free survival in advanced ovarian cancer using Affymetrix Human Exon 1.0 ST arrays in 2011 by Sabatier *et al*. Out of seven genes, five genes (SLC7A2, ALCAM, TMPRSS3, TSPAN6, and C14orf101) expression was associated with better survival chances and the expression of two genes (A1BG and PAH) was associated with bad prognosis.[40] In 2012, a validated gene profile involved in the repair of platinum-induced DNA damage was developed with a prognostic scoring system categorizing advanced ovarian carcinoma into low- and high-risk groups. Based on the expression of 23 genes, a score of 0-20 was assigned. A score of 0-10 was considered low risk and 11–20 was the high-risk group. The low-risk group responded well to chemotherapy with platinum and had a long disease-free survival. However, it was not validated in a prospective trial.[41] In 2013, the Classification of Ovarian Cancer (CLOVAR), a prognostic 100-gene signature that is a combination of subtype and survival gene expression, was introduced after validation. The high-grade ovarian cancer was stratified into low-, intermediate-, and high-risk groups by computing scores of three survival signature models. The first model was the CLOVAR survival score and CLOVAR subtype signatures by which tumors were classified into CLOVAR immunoreactive, CLOVAR mesenchymal, and others. The second model was developed by adding age, grade, stage, and residual disease to the second model. The third model, a combination of BRCA1/BRCA2 germline mutation status and the second model.[42] The previous studies were not able to establish survival differences between the molecular subtypes. However, in 2014, Konecny *et al*. did a small-scale study using an Agilent array in advanced serous carcinoma of the ovary with prespecified TCGA Network gene signatures. A long-term follow-up of 174 patients was carried out. The study concluded that the immunoreactive subtype has better survival chances in comparison to the proliferative or mesenchymal subtypes.[43] In 2016, two transcriptome classes (I and II) were developed and validated in rare histological ovarian cancer types, endometrioid carcinoma, clear cell carcinoma, mucinous carcinoma, and low-grade serous carcinoma. The class-1 tumor had better survival than

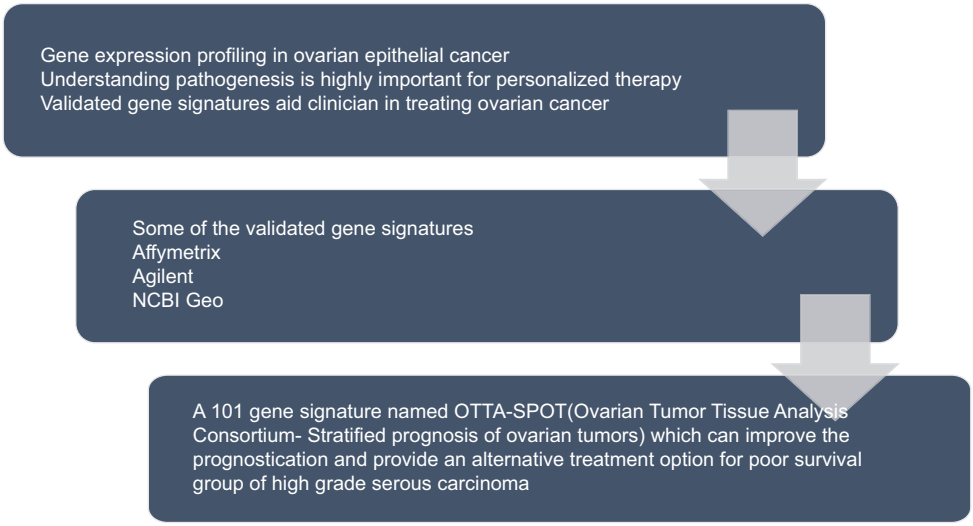

Figure 1: Summary of the gene expression profiling in ovarian epithelial cancer

class-II. A pathway enrichment analysis revealed enriched WNT signaling pathway and steroid production in class-I, whereas class-II had activated toll-like receptor and cell cycle signaling pathways.[44] A breakthrough in the chemoresponse of advanced ovarian cancer was seen by the development of a 97-gene signature based on HIF1α and TP53 expressions.[45] Recently, a small panel of 8-gene signatures related to energy metabolism was developed comprising two protective genes CCR7 and IFI27 as well as six risk factor genes TLL1, COL16A1, PTGFR, CILP2, KIF26B, and GAS1. The gene signature related to energy metabolism was able to predict the overall survival in ovarian cancer paving the way to develop a predictive test for clinical utility.[46] A ray of hope has been instilled in the treatment of ovarian cancer with the development of a 101-gene signature named the Ovarian Tumor Tissue Analysis Consortium–Stratified Prognosis of Ovarian Tumors which can improve the prognostication and provide an alternative treatment option for poor survival group of high-grade serous carcinoma patients as it is enriched in pathways with treatment ramifications.[47]

Summary

Summarized in Figure 1.

Conclusion

Microarray investigations can contribute to the search for novel therapeutic options in EOC. Gene expression-based tools for the prediction of patient prognosis after surgery or chemotherapy are currently available for some cancers like MammaPrint to predict the likelihood of metastasis in breast cancer. Similarly, the Oncotype Dx assay is also available for colon and prostate cancer. The development of a similar tool for ovarian cancer will greatly improve the patient's prognosis and quality of life. Our study provides information for researchers to identify possible candidate genes and pathways that may be involved in EOC for further studies.

Author Contributions

Conceptualization, Concept designed by Dr Banushree; Methodology, PRISMA was used to generate articles in search engine by Dr Banushree & Dr Subhashini; Resource, Generated by Pubmed and authentication done by Dr Banushree & Dr Subhashini; Writing – Original Draft Preparation, Written by Dr Banushree & Dr Subhashini; Writing – Review & Editing, Done By Dr Banushree; Supervision, by Dr Banushree; All authors have read and agreed to the final version of the manuscript.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

There are no conflicts of interest.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Coburn SB, Bray F, Sherman ME, Trabert B. International patterns and trends in ovarian cancer incidence, overall and by histologic subtype. Int J Cancer 2017;140:2451-60.
3. Jacobs IJ, Menon U. Progress and challenges in screening for early detection of ovarian cancer. Mol Cell Proteomics 2004;3:355-66.
4. Badgwell D, Bast RC Jr. Early detection of ovarian cancer. Dis Markers 2007;23:397-410.
5. Momenimovahed Z, Tiznobaik A, Taheri S, Salehiniya H. Ovarian cancer in the world: Epidemiology and risk factors. Int J Womens Health 2019;11:287-99.
6. Rojas V, Hirshfield KM, Ganesan S, Rodriguez-Rodriguez L. Molecular characterization of epithelial ovarian cancer: Implications for diagnosis

and treatment. Int J Mol Sci 2016;17:2113.
7. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: A review. Cancer Biol Med 2017;14:9-32.
8. Terada KY, Ahn HJ, Kessel B. Differences in risk for type 1 and type 2 ovarian cancer in a large cancer screening trial. J Gynecol Oncol 2016;27:e25.
9. Kehoe S. FIGO staging in ovarian carcinoma and histological subtypes. J Gynecol Oncol 2020;31:e70.
10. Berek JS, Kehoe ST, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet 2018;143 Suppl 2:59-78.
11. Konecny GE, Winterhoff B, Wang C. Gene-expression signatures in ovarian cancer: Promise and challenges for patient stratification. Gynecol Oncol 2016;141:379-85.
12. Kupryjańczyk J, Madry R, Plisiecka-Hałasa J, Bar J, Kraszewska E, Ziółkowska I, *et al.* TP53 status determines clinical significance of ERBB2 expression in ovarian cancer. Br J Cancer 2004;91:1916-23.
13. Schaner ME, Ross DT, Ciaravino G, Sorlie T, Troyanskaya O, Diehn M, *et al*. Gene expression patterns in ovarian carcinomas. Mol Biol Cell 2013;14:4376-86.
14. Januchowski R, Wojtowicz K, Sujka-Kordowska P, Andrzejewska M, Zabel M. MDR gene expression analysis of six drug-resistant ovarian cancer cell lines. Biomed Res Int 2013;2013:241763.
15. Ying H, Lv J, Ying T, Li J, Yang Q. Screening of feature genes of the ovarian cancer epithelia with DNA microarray. J Ovarian Res 2013;6:39.
16. Tothill RW, Tinker AV, George J, Brown R, Fox SB, Lade S, *et al.* Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. Clin Cancer Res 2008;14:5198-208.
17. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature 2011;474:609-15.
18. Tan TZ, Miow QH, Huang RY, Wong MK, Ye J, Lau JA, *et al.* Functional genomics identifies five distinct molecular subtypes with clinical relevance and pathways for growth control in epithelial ovarian cancer. EMBO Mol Med 2013;5:1051-66.
19. Denkert C, Budczies J, Darb-Esfahani S, Györffy B, Sehouli J, Könsgen D, *et al*. A prognostic gene expression index in ovarian cancer – Validation across different independent data sets. J Pathol 2009;218:273-80.
20. Helland Å, Anglesio MS, George J, Cowin PA, Johnstone CN, House CM, *et al.* Deregulation of MYCN, LIN28B and LET7 in a molecular subtype of aggressive high-grade serous ovarian cancers. PLoS One 2011;6:e18064.
21. Mok SC, Bonome T, Vathipadiekal V, Bell A, Johnson ME, Wong KK, *et al*. A gene signature predictive for outcome in advanced ovarian cancer identifies a survival factor: Microfibril-associated glycoprotein 2. Cancer Cell 2009;16:521-32.
22. Schwede M, Waldron L, Mok SC, Wei W, Basunia A, Merritt MA, *et al.* The impact of stroma admixture on molecular subtypes and prognostic gene signatures in serous ovarian cancer. Cancer Epidemiol Biomarkers Prev 2020;29:509-19.
23. Köbel M, Bak J, Bertelsen BI, Carpen O, Grove A, Hansen ES, *et al.* Ovarian carcinoma histotype determination is highly reproducible, and is improved through the use of immunohistochemistry. Histopathology 2014;64:1004-13.
24. Kurman RJ, Shih IE. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer – Shifting the paradigm. Hum Pathol 2011;42:918-31.
25. Fekete T, Rásó E, Pete I, Tegze B, Liko I, Munkácsy G, *et al.* Meta-analysis of gene expression profiles associated with histological classification and survival in 829 ovarian cancer samples. Int J Cancer 2012;131:95-105.
26. Russo G, Zegar C, Giordano A. Advantages and limitations of microarray technology in human cancer. Oncogene 2003;22:6497-507.
27. Li H, Wang X, Fang Y, Huo Z, Lu X, Zhan X, *et al.* Integrated expression profiles analysis reveals novel predictive biomarker in pancreatic ductal adenocarcinoma. Oncotarget 2017;8:52571-83.
28. Wang Z, Yang B, Zhang M, Guo W, Wu Z, Wang Y, *et al.* lncRNA Epigenetic landscape analysis identifies EPIC1 as an oncogenic lncRNA that interacts with MYC and promotes cell-cycle progression in cancer. Cancer Cell 2018;33:706-20.e9.
29. Spentzos D, Levine DA, Ramoni MF, Joseph M, Gu X, Boyd J, *et al.* Gene expression signature with independent prognostic significance in epithelial ovarian cancer. J Clin Oncol 2004;22:4700-10.
30. Marquez RT, Baggerly KA, Patterson AP, Liu J, Broaddus R, Frumovitz M, *et al.* Patterns of gene expression in different histotypes of epithelial ovarian cancer correlate with those in normal fallopian tube, endometrium, and colon. Clin Cancer Res 2005;11:6116-26.
31. Berchuck A, Iversen ES, Lancaster JM, Pittman J, Luo J, Lee P, *et al.* Patterns of gene expression that characterize long-term survival in advanced stage serous ovarian cancers. Clin Cancer Res 2005;11:3686-96.
32. Jazaeri AA, Awtrey CS, Chandramouli GV, Chuang YE, Khan J, Sotiriou C, *et al.* Gene expression profiles associated with response to chemotherapy in epithelial ovarian cancers. Clin Cancer Res 2005;11:6300-10.
33. Bonome T, Levine DA, Shih J, Randonovich M, Pise-Masison CA, Bogomolniy F, *et al*. A gene signature predicting for survival in suboptimally debulked patients with ovarian cancer. Cancer Res 2008;68:5478-86.
34. Wang PH. The role of laparoscopy and the value of peritoneal carcinomatosis index in patients with intra-abdominal malignancies who are scheduled to laparotomy. Gynecol Minim Invasive Ther 2019;8:51-2.
35. Tantitamit T, Lee CL. Is it the time for laparoscopic management of early-stage ovarian malignancies? Gynecol Minim Invasive Ther 2018;7:93-103.
36. Palakkan S, Augestine T, Valsan MK, Vahab KP, Nair LK. Role of frozen section in surgical management of ovarian neoplasm. Gynecol Minim Invasive Ther 2020;9:13-7.
37. Crijns AP, Fehrmann RS, de Jong S, Gerbens F, Meersma GJ, Klip HG, *et al.* Survival-related profile, pathways, and transcription factors in ovarian cancer. PLoS Med 2009;6:e24.
38. Zhou Y, Cheng Z. The roles of microRNA-133 in gynecological tumors. Gynecol Minim Invasive Ther 2022;11:83-7.
39. Konstantinopoulos PA, Spentzos D, Karlan BY, Taniguchi T, Fountzilas E, Francoeur N, *et al.* Gene expression profile of BRCAness that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer. J Clin Oncol 2010;28:3555-61.
40. Sabatier R, Finetti P, Bonensea J, Jacquemier J, Adelaide J, Lambaudie E, *et al*. A seven-gene prognostic model for platinum-treated ovarian carcinomas. Br J Cancer 2011;105:304-11.
41. Kang J, D'Andrea AD, Kozono D. A DNA repair pathway-focused score for prediction of outcomes in ovarian cancer treated with platinum-based chemotherapy. J Natl Cancer Inst 2012;104:670-81.
42. Verhaak RG, Tamayo P, Yang JY, Hubbard D, Zhang H, Creighton CJ, *et al.* Prognostically relevant gene signatures of high-grade serous ovarian carcinoma. J Clin Invest 2013;123:517-25.
43. Konecny GE, Wang C, Hamidi H, Winterhoff B, Kalli KR, Dering J, *et al.* Prognostic and therapeutic relevance of molecular subtypes in high-grade serous ovarian cancer. J Natl Cancer Inst 2014;106:dju249.
44. Wang C, Winterhoff BJ, Kalli KR, Block MS, Armasu SM, Larson MC, *et al.* Expression signature distinguishing two tumour transcriptome classes associated with progression-free survival among rare histological types of epithelial ovarian cancer. Br J Cancer 2016;114:1412-20.
45. Matondo A, Jo YH, Shahid M, Choi TG, Nguyen MN, Nguyen NN, *et al.* The prognostic 97 chemoresponse gene signature in ovarian cancer. Sci Rep 2017;7:9689.
46. Wang L, Li X. Identification of an energy metabolism-related gene signature in ovarian cancer prognosis. Oncol Rep 2020;43:1755-70.
47. Millstein J, Budden T, Goode EL, Anglesio MS, Talhouk A, Intermaggio MP, *et al*. Prognostic gene expression signature for high-grade serous ovarian cancer. Ann Oncol 2020;31:1240-50.
48. Yoshihara K, Tajima A, Yahata T, Kodama S, Fujiwara H, *et al*. Gene Expression Profile for Predicting Survival in Advanced-Stage Serous Ovarian Cancer Across Two Independent Datasets. PLoS ONE 2010; 5:e9615.
49. Fei H, Chen S, Xu c. Bioinformatics analysis of gene expression profile of serous ovarian carcinomas to screen key genes and pathways. J of Ovar Res 2020;13:1-12.