Role of DNA methylation and non-coding RNAs expression in pathogenesis, detection, prognosis, and therapy-resistant ovarian carcinoma (Review)

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Abstract. Ovarian cancer is the deadliest gynecological cancer globally, with epithelial ovarian cancer (EOC) comprising up to 90% of cases. A molecular characterization linking the histological subtypes with tumor grade in EOC has been suggested. Variations in genetic biomarkers such as BRCA1/2, MSH2, MLH1/6, BRIP1, and RAD51C/D have been studied in EOC. In addition, molecular characteristics, including DNA methylation and RNA transcription, are being explored as potential new biomarkers for the diagnosis and prognosis of this type of neoplasia. The present review focused on the role of DNA methylation and non-coding RNA expression in the development of ovarian carcinomas and their association with diagnosis, prognosis, and the resistance of cancer cells to radiotherapy and chemotherapy. The present review considered the transition from the DNA structure to the RNA expression in ovarian carcinoma.

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1. Introduction

Ovary cancer (OC) is considered the most lethal malignancy among gynecological cancers. In 2020 worldwide, OC caused 1.6% of all new cancer-related deaths (1). Epithelial ovarian cancer (EOC) is a clinical type of OC that is already diagnosed in 90% of women patients with OC; patients with this OC type are typically diagnosed in the advanced stages of the disease (75%) when cancer has disseminated to a different abdominal tissue or metastases are present. The majority of patients (>70%) with advanced-stage OC do not respond to standard therapies, resulting in a resistant, fatal disease (2). Due to this, the identification and understanding of the molecular characteristics associated with early disease progression, prediction and clinical responses are necessary to improve survival and clinical treatment in women with EOC.

In this regard, differential cancer DNA methylation, compared with the origin tissue cells, is an early event during carcinogenesis. That is, DNA methylation is composed of concomitant global unmethylated DNA and local locus-methylated DNA. Methylated DNA consists of the addition of a methyl group in the fifth carbon of cytosine residues, forming a CpG; this addition forms 5-methylcytosine. Typical examples of DNA-methylation phenotypes have been characterized in certain types of cancer, such as colorectal carcinoma, breast carcinoma and glioma (3-8). Methylated DNA molecules are more compact than unmethylated DNA molecules (3). It has been proposed that unmethylated DNA is a characteristic of cancer while methylated DNA presents only a variable consequence depending on the locus and on the specific part of the locus in cancer cells (9,10). RNA transcription is strongly

influenced by DNA methylation. Methylated loci are silenced and unmethylated loci are transcriptionally activated in ovarian carcinoma tumors. The diagnosis of patients is made by transvaginal ultrasound and detection of cancer antigen (CA)-125 levels; however, the state of DNA methylation and RNA expression in the tumors has been currently associated with the diagnosis of the histological subtypes in the different types of ovarian carcinoma, the advanced stages and, importantly, the survival of the patients.

EOC is a heterogeneous carcinoma type and every EOC subtype has its natural history of development. Specifically, cell subtypes are described by histopathological and molecular characteristics of ovarian carcinoma (11-13). However, it is considered that serous ovarian carcinomas are developed as a disease continuum, from low-grade to high-grade serous ovarian carcinomas. Evidence suggests that high-grade and low-grade serous carcinomas develop independently in their natural course of progression and they have different prognoses (12,13).

At the molecular level, the prognosis of spontaneous EOC type I and type II is associated with the EOC sub-type, the age of the patient and the treatment used. Although advances in clinical treatments have increased in the past few decades, the pathology structure remains unaltered (14). Of patients diagnosed with ovarian cancer, ~50% survive five years following diagnosis, including 29% of those with metastases of ovarian carcinoma (1). In ovarian carcinomas, several factors determine survival, including primarily histological subtype, grade, stage, cytoreductive surgery and, secondarily, ethnicity (15,16).

The mortalities associated with ovarian cancer comprise 4% of all cancer-related deaths (1,14). Germinal variations are changes in DNA locus. Germinal variants of ovarian carcinomas are present in 5% of patients with ovarian carcinoma. Ovarian carcinomas are mutated in the following two ways: In germinal DNA (DNA variants of hereditary cancer origin) or in somatic DNA (DNA variants with individual spontaneous tumor cancer origin). Variants in the germ line DNA represent 24% of OC. The majority of the genetic variants are present in BRCA in hereditary breast and ovarian cancer syndrome (HBOC), whereas other DNA repair genes are present in Lynch syndrome (LS), also called hereditary non-polyposis colorectal cancer syndrome (17).

The loci mutations with higher hereditary penetrance to develop ovarian carcinoma are those of *BRCA1* or *BRCA2*. HBOC accounts for ~80% of hereditary ovarian carcinoma and 15% of epithelial OC cases. In HBOC, 65-85% of cancers are due to genomic variants in *BRCA1* and *BRCA2* genes, which are considered high penetrance for OC (18). These genes encode proteins for homologous recombination to repair DNA double-strand breaks and maintain genomic stability. In addition, germinal carcinoma with BRCA1/2 mutations develops a high-grade serous ovarian carcinoma (HGSOC) subtype (15,16,19). Other loci mutations with moderate familial penetrance involve genes implicated in OC, such as *BARD1, BRIP1, PALB2, RAD50*, *RAD51C, NBN and MRE11A;* these mutations are encoded in each gene that has been involved in OC as part of the *BRCA2*/Fanconi anemia signaling pathway (20). Epithelial OC deficiency in DNA mismatch repair is the second most common cause of HBOC, accounting for 10-15% of this condition. The lifetime risk of developing OC with LS is ~8-12% and the mean age at presentation is ~43 years. OC-associated genes in this pathway are the following: *MLH1, MSH2, MSH6* and *PMS2*. Specifically, *BRIP1*, *MLH1, MSH2, MSH6*, *PMS2* and *EPCAM* are moderate penetrance genes in OC (16-19).

It is notable that each mutated locus develops different characteristics in the phenotype of tumor cells present in the patients (19-23). By contrast, EOCs developed from a somatic spontaneous origin are heterogeneous. At the cellular level, ovarian carcinoma tumors are classified into five different types: HGSOC, low-grade serous ovarian carcinoma (LGSOC), mucinous carcinoma (MC), clear cells carcinoma (CCC) and endometrioid carcinoma (EC). Recently, DNA methylation and RNA transcription have been shown to vary in a defined way to develop EOC tumors, such as hypomethylated DNA and variation in RNA expression. It is notable that germinal variation in the DNA locus of the large non-coding RNA (lncRNA) *HOTAIR* is a risk cause of developing ovarian carcinoma. In addition, overexpression of *HOTAIR* has been found in ovarian carcinomas and it has been associated with chemotherapy resistance (24).

Ovarian carcinoma, which is resistant to radiotherapy and chemotherapy is another important problem. For example, in HGSOC, the presence of the *TP53* mutation and chromosome instability (CIN) are associated with resistance to radiotherapy and standard chemotherapy, which is a mix of carboplatin and taxane (25). In addition, it has been observed that DNA methylation loci induce sensitivity to therapies. By contrast, the DNA methylation loci of the nuclear RNA transcripts are associated with resistance to treatment. In this regard, it has been proposed that ovarian carcinoma cells could be sensitized to radiotherapy and chemotherapy by the addition of DNA methylation inhibitors such as decitabine (25).

2. DNA methylation in the diagnoses of ovarian carcinomas

The molecular characteristics validate the natural history of ovarian carcinoma tumors and explain the association between clinical characteristics of ovarian carcinoma, such as mutations in the expression levels of DNA, RNA and proteins with patient survival. The first characterization of ovarian carcinoma is performed by quantifying transvaginal CA-125 levels using ultrasonic waves (26). Subsequently, the characterization of the macroscopic tumors in surgery is required and finally the histological characteristics have to be defined by microscopic observations. Finally, the characterization of the genotype is proposed using nuclear characteristics to improve diagnosis and prognosis, as well as to confirm the natural history of the tumors. This is due to the phenotype of the tumor cells being associated with DNA methylation. Unmethylated DNA has been associated with nuclear size, aneuploidy, carcinoma subtypes and higher proliferation of ovarian carcinoma cells (27,28) [Table I, (29-48)].

Currently, the following examples have been demonstrated that indicate the DNA methylation status of ovarian carcinomas and describe the hypomethylated nuclear locus in the tumors compared with that of ovarian epithelial cells: The global loci markers (satellite sequences and *ALU* repetitive sequences) and the local loci markers. The assays used to discriminate the state of methylation currently available in human tumors are the following: Sodium bisulfite DNA treatment and pyrosequencing, reverse transcription-quantitative PCR (RT-qPCR), or methylation-specific PCR. High-resolution methods to

Table I. Characterization of DNA methylation *loci* in ovarian carcinomas.

First author/s, year	Ovarian carcinoma subtype	*Locus* chromosome	Gene on the *locus*	Methods	Status in ovarian carcinoma	(Refs.)
Feng *et al*, 2008	EOC	*3q13.33* and *19q13.43*	*ARH1* and *PEG3*	Sodium bisulfite and pyrosequencing	Hypermethylated	(29)
Link *et al*, 2013	EOC	*20q13.31*	*BORIS/ CTCFL*	Sodium bisulfite and pyrosequencing	Unmethylated	(30)
Wang *et al*, 2013	EOC	*17q21.31*	*BRCA1*	Sodium bisulfite and RT-qPCR	Hypermethylated	(31)
Abou-Zeid *et al*, 2011; Bhagat *et al*, 2014	EOC	*9p21.3*	*CDKN2A*	Sodium bisulfite and RT-qPCR	Hypermethylated	(32,33)
Yang *et al*, 2013	EOC	*8p21.1*	*Clusterin*	Sodium bisulfite and RT-qPCR	Unmethylated	(34)
Zhang *et al*, 2015	EOC	*Xq26.3*	*CT45*	Sodium bisulfite and pyrosequencing	Unmethylated	(35)
Wang *et al*, 2017	EOC	*11q25*	*OPCML*	Sodium bisulfite and RT-qPCR	Hypermethylated	(36)
Kaur *et al*, 2016	EOC	*9q21.33 and 13q34*	*DAPK1 and SOX1*	Sodium bisulfite and RT-qPCR	Hypermethylated	(37)
Rattanapan *et al*, 2018	HGSOC	*9q34.3*	*EGFL7*	Sodium bisulfite and pyrosequencing	Hypermethylated	(38)
da Conceição Braga *et al,* 2014	EOC	*18q21.33 and 8p21.3*	*BCL2* and *TRAIL2-R2*	Sodium bisulfite and RT-qPCR	Hypermethylated	(39)
Bonito *et al*, 2016	EOC	*4p16.2*	*MSX1*	Sodium bisulfite and RT-qPCR	Hypermethylated	(40)
Kardum *et al*, 2017; Suzuki *et al*, 2008	EOC	*14q23.2*	*ER-β*	Sodium bisulfite and RT-qPCR. Sodium bisulfite and pyrosequencing	Hypermethylated	(41,42)
Baranova *et al*, 2018	HGSOC	*13q21.1*	*PCDH17*	Sodium bisulfite and RT-qPCR. Sodium bisulfite and pyrosequencing	Hypermethylated	(43)
Ding *et al*, 2016	EOC	*11p14.3*	*FANCF*	Sodium bisulfite and pyrosequencing	Hypermethylated	(44)
Gozzi *et al*, 2016	EOC	*1p12*	*TBX15*	Sodium bisulfite and pyrosequencing	Hypermethylated	(45)
Choi *et al*, 2006	EOC	*3p21.31*	*RASSF1A*	Sodium bisulfite and RT-RT-qPCR	Hypermethylated	(46)
Häfner *et al*, 2016	EOC	*1p36.11 and 1p36.12*	*RUNX3 and CAMK2N1*	Sodium bisulfite and RT-qPCR	Hypermethylated	(47)
Jin *et al*, 2018	EOC	*3p14.3*	*Wnt5a*	Sodium bisulfite and RT-qPCR	Hypermethylated	(48)

EOC, epithelial ovarian cancer; HGSOC, high-grade serous ovarian carcinoma; RT-qPCR, reverse transcription-quantitative PCR.

determine cell single DNA methylation are currently available, such as droplet and digital PCR (43-50).

DNA methylation and RNA expression are associated with ovarian carcinoma cells. This indicates that RNA transcription could be inhibited due to the DNA methylation status of the locus, except for certain recent paradoxical examples led by a negative correlation in other types of cancers, where intragenic methylation correlates with gene overexpression (Table II) (51,52). In contrast to these observations, RNA expression is activated in the unmethylated DNA status of the locus (9). Therefore, RNA transcription is differentially present in ovarian carcinoma. MicroRNAs (miRs) are a class of

Table II. Hyper-methylated miRNAs locus in ovarian carcinoma.

Locus chromosome	Non-coding RNA expressed in locus	DNA status methylation in locus	RNA expression of locus
11q24.1	*miR-125-1*	Hypermethylated	Downregulated
14q32.2	*miR-127*	Hypermethylated	Downregulated
11p11.2	*miR-129-2*	Hypermethylated	Downregulated
1p21.3	*miR-137*	Hypermethylated	Downregulated
17q11.2	*miR-193a*	Hypermethylated	Downregulated
14q32.2	*MEG3*	Hypermethylated	Downregulated

miR, microRNA. All dates referenced in this table from (53).

small RNA transcripts (19-22 nucleotides) that decrease gene expression via translational inhibition or degradation of target messenger RNA (mRNA). Various miRs are differentially expressed in cancer, suggesting a link between these molecules and the different expression levels of proteins in cancer tissues (53). By contrast, large non-coding RNAs (lncRNAs) function on affecting the nuclear structure and RNA transcription. It is notable that the hypermethylated DNA of RNA loci decrease the presence of miRs and MEG3 (53-55), which is a lncRNA, so that the RNA transcripts in the normal ovarian tissue, benign epithelial tumors, benign epithelial ovarian cysts, malignant ovarian carcinoma and serous ovarian carcinoma exhibit differential expression of RNA transcripts (56-59).

It remains to be determined why DNA methylation in ovarian carcinomas is heterogeneous. In 2014, the World Health Organization classification guidelines for female reproductive tumors defined the ovarian carcinoma type in cell-level characterized ovarian carcinoma subtypes HGSOC, LGSOC, CCC, MC and EC (11-13,21,60). It was proposed that at the molecular level, the natural history of ovarian carcinomas is HGSOC. A fallopian tube epithelial origin was found when DNA methylation was compared (61,62). HGSOC has locally DNA methylations in 6 loci that differentiate HGSOC from the OSE DNA methylation pattern (*ARMCX1*, *ICAM4*, *LOC134466*, *PEG3*, *PYCARD* and *SGNE1*) (41); HGSOC overexpresses miR-223, miR-551b-3p, miR-30a-5p, miR-9 and miR-30a-5p (63-70). Other studies using miR microarrays have described the different expression patterns of serous ovarian carcinoma (70) and clear cell carcinoma (CCC), specifically the *SFRP1* methylated locus (41,71,72). By contrast, DNA methylation in low-grade serous ovarian carcinoma has not been reported to date compared with other ovarian carcinoma subtypes or epithelial ovarian cells. By contrast, it has been shown that endometrioid carcinoma (EC) has similarities with endometrial and ovarian carcinomas in the promoter hypermethylated locus (73-76). CCC has been characterized by the HNF1 pathway to be unmethylated, whereas the RE alpha pathway is unmethylated, similar to OSE (71). Finally, mucinous carcinomas (MUC) exhibit 81 unmethylated genes that are different from those of HGSOC. It is notable that MUC-DNA methylation is more similar to colorectal and stomach carcinoma than HGSOC, providing additional information on the MUC origins from colorectal metaplasia (12,77). Downregulation of miR-192 and miR-2215 levels is also noted in MUC (78) (Fig. 1).

In conclusion, DNA methylation is a characteristic that varies early in the development of ovarian carcinoma cells. The vestige of a methylated locus in the origin tissues of ovarian carcinomas marks a directional methylation of every ovarian carcinoma subtype. DNA methylation and RNA expression are associated. Finally, DNA methylation and RNA transcripts are associated and differentially presented by the subtype cells.

DNA methylation and ncRNA expression as prognostic biomarkers of ovarian carcinomas. The following factors are associated with the prognosis of patients with ovarian carcinoma: The variations in DNA syndromes, the ethnic origin, the origin of the gynecological pathologies, the subtypes, the advanced stages of the tumors (metastasis to lymph node, or metastasis to distant tissues), the size of residual tumor following cytoreductive surgery and the resistance of cancer cells to radiotherapy and chemotherapy. It is notable that 75% of ovarian carcinomas are of HGSOC sub-type and the patient 5-year survival following diagnosis with ovarian carcinoma is ~47%. In comparison, the survival of the women diagnosed with metastasis of ovarian carcinoma is only 29% (11,15,21-23,79,80).

The RNA expression could be driven by a random accumulation or by a directional and defined development as determined by the stages of International Federation of Gynecology and Obstetrics (FIGO) (81) in every molecular ovarian carcinoma subtype. Several pieces of evidence have concluded that RNA transcripts are overexpressed and downregulated in a directional way (Tables II and III). First, this has been presented in the diagnosis biomarkers without poor prognosis. Except for the *BRCA1/2* mutation and the DNA methylation locus associated with response to chemotherapy, the RNA transcripts are not related to the prognosis of the patients or the single nucleotide polymorphism in *HOXA11* that protects cells from developing HGSOC (82). This suggests that biologically, hereditary mutations have a higher risk weight than DNA methylation or RNA expression, which are more sensitive to alterations of the phenotype state but not of the patient's outcome. The nuclear characteristics determined of the advanced FIGO stages of ovarian carcinoma are CIN, DNA methylated locus in genes, such as *BRCA1*, *FANCF*, *RASSF1A* and *Wnt5A*, the downregulated levels of TUBA14B and the overexpressed RNA transcripts of the following genes and lncRNAs: *MGMT*, *OSMR*, *ESR1* and *FOXL2* and long non-coding (lnc)*BRM*, *HOTAIR*, *HOXDAS-1* and *lncSOX4* and *CPS1-IT1* (83-87) (Table IV).

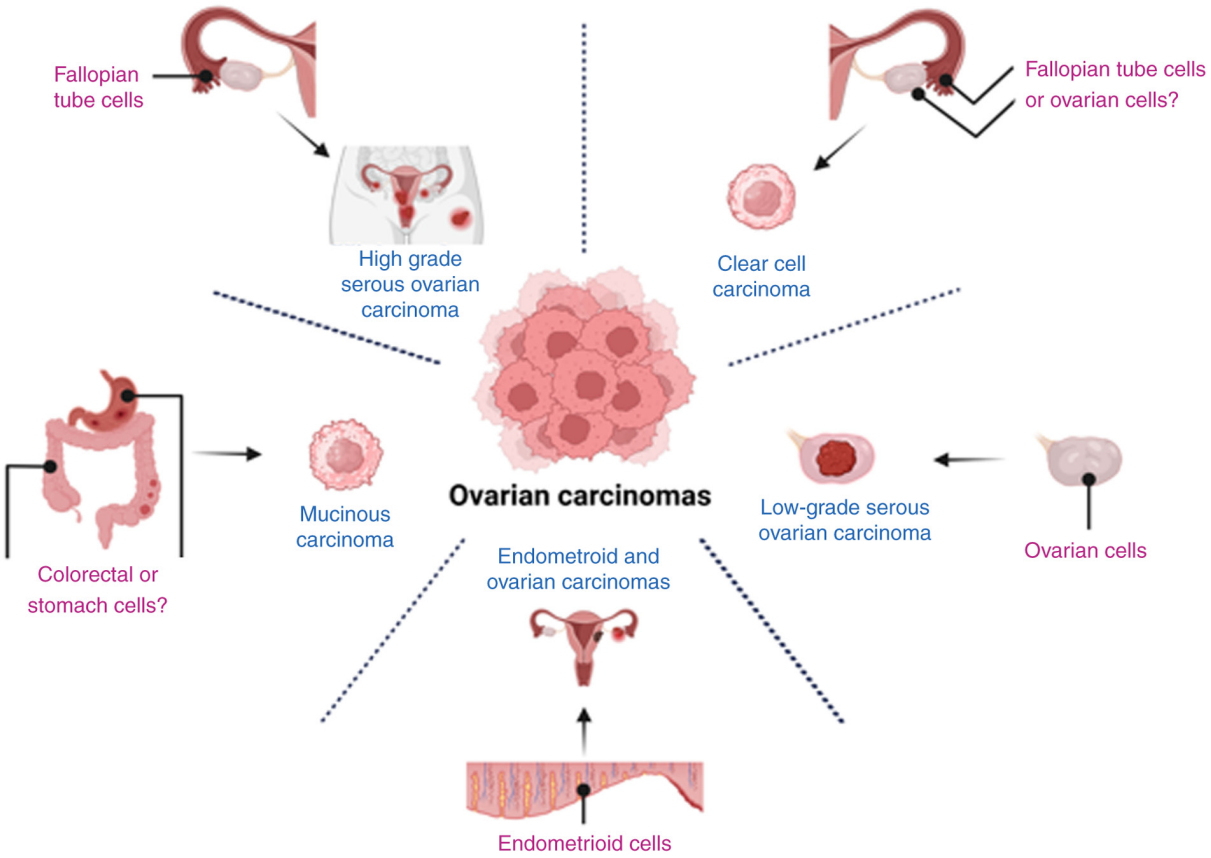

Figure 1. Natural history of ovarian carcinoma. Ovarian carcinoma is a heterogeneous type of cancer. Five subtypes of ovarian carcinomas originate in different forms. Origin tissues are enlisted in the periphery of the image and ovarian carcinomas are enlisted near the image core, similar to the nuclear ovarian carcinoma archetype. The transformation of the cells of the ovarian carcinoma origin can be described as follows: Fallopian tube cells originate HGSOC. Superficial cells of the ovary originate CCC. The origin of colorectal or stomach cells that develop in MC remains to be determined due to their tissue similitudes Endometrial cells originate EC. Fallopian tube cells or ovary cells originate LGSOC. Created by BioRender.com. Accessed on 09/2024. HGSOC, high-grade serous ovarian carcinoma; CCC, clear cell carcinoma; LGSOC, low-grade serous ovarian carcinoma; EC, endometrioid carcinoma; MC, mucinous carcinoma.

The assays used to analyze RNAs are transcriptomics or expression analysis of single locus transcription detected by RT-qPCR (88,89). It is notable that the overexpressed and downregulated transcripts associated with tumor development classified by FIGO stages could probably result in equilibration of their levels in the nuclear structure; in addition, the variation in transcript levels within patients has to be taken into account; for example, the levels of *MLK7-AS1* and *TUG1* were increased 2.5- and 2.2-fold, respectively; the levels of *CASC2* were diminished 0.6-fold compared with the relative expression noted in advanced stage ovarian carcinoma cells (90-98). These types of variation in the RNA expression levels are individual assessments in ovarian carcinoma subtypes derived from a population, which are defined by comparison of the expression levels of their corresponding counterparts. However, in the majority of the studies, the ovarian cancer cells are used as a point of calibration (66,67,98-162).

Patients with advanced stages have methylated loci DNA on *ER*-b, *RUNX3*, and *CAMK2N1*; these alterations have been associated with poor prognosis (41-43). The lncRNAs *SPRY4-IT1* and *HOXA11* are associated with ovarian carcinoma transformation; they are overexpressed in ovarian carcinoma compared with ovarian untransformed cells (107,108,163-184). In addition, overexpression of the miR-200 family members and MALAT1 have been associated with poor prognosis in advanced stages with a sensitivity of 88%; specifically miR-125b overexpression exhibits a sensitivity of 75.6% (108,172,181-185). In addition, miR-199a exhibits a sensitivity of 72% related to positive lymph node metastasis (154,186-189). Moreover, miR-125b overexpression exhibits a sensitivity of 72%, which is characteristic of ovarian carcinoma, associated with 67% grade, 77% positive lymph node metastasis and 89% metastasis (190). The upregulation of the expression of *CPST1-IT1* is also associated with cancer, stage and lymph node metastasis with a hazard ratio of 3.257 (P=0.004) (97). This suggests a variation in the gradual overexpression during the development of ovarian carcinomas. RNA transcripts have a directional variation of expression during the development of the natural history of ovarian carcinomas, which is initiated from the tissues of origin (Fig. 2).

The molecular-resistant ovarian carcinoma. Molecular and cellular biology allows the improved understanding of the microscopic and macroscopic observations of ovarian carcinomas. The selection of the therapeutic methods, such as surgery, radiotherapy and chemotherapy, depends on several factors, such as the carcinoma grade, FIGO stage and patient characteristics, namely age (81). Surgery is performed to obtain

Table III. microRNAs expression associated with cancer functions derived from *locus* and target locus RNAs probed in specific ovarian carcinoma subtypes.

First author/s, year	Ovarian carcinoma subtype	Associated with	*Locus* of the miRNA	microRNA	RNA regulation	*Locus* of the target	RNA from the locus target	(Refs.)
Nymoen *et al*, 2016	EOC	Poor prognosis	*7q32.3*	29a	Down	*2p23.3*	DNMT3A	(66)
Arts *et al*, 2017	HGSOC	HGSOC	*Xq12*	223	Up	*12q13.12*	SMARCD1	(67)
Ying *et al*, 2016	EOC	Poor prognosis, clinical stage III and IV clinical grade	*11q24.1*	125b	Down	*9q34.11*	SET	(99)
Zhu *et al*, 2017	EOC	II and III lymph node metastasis distant metastasis	*11q24.1*	125b	Up	*9q34.11*	SET	(100)
Teng *et al*, 2015	EOC	Poor prognosis	*1p36.33*	29b	Down	*1q21.2, 19q13.2 and 1q43*	Mcl-1, AKT2 and AKT3	(101)
Cao *et al*, 2015; Katepanakis *et al*, 2015; Meng *et al*, 2016	EOC	Poor prognosis stage grade	*1p36.33*	200a/ 200b/ 200c	Up			(102-104)
Du *et al*, 2017	EOC	EOC	*12p13.31*	551a	Down	*22q11.22/ 14q32.33*	MAPK/ AKT	(105)
Chaluvally-Raghavan *et al*, 2016	EOC	Poor prognosis	*1p36.32*	551b-3p	Up	*17q21.2*	STAT3	(68)
Chen *et al*, 2015	EOC	Advanced stages High grade	*3q26.2*	490-3p	Up	*10q21.2*	CDK1	(106)
Shuang *et al*, 2015	EOC	Chemotherapy resistant	*14q32.31*	134	Down	*3q29*	Pak2	(107)
Zou *et al*, 2015	EOC	Stage histology	*15q24.1*	630	Down	*10q23.31*	PTEN	(108)
Zhang *et al*, 2016	EOC	EOC	*5q32*	143-3p	Down	*18p11.22*	RALBP1	(109)
Zhang *et al*, 2018	EOC	Stage lymph node metastasis	*21q21.1*	Let-7c	Down	*3p21.31*	CDC25a	(110)
Liu *et al*, 2014	EOC	Poor prognosis stage	*9q34.11*	199b-5p	Down	*20p12.2-9q34.3*	JAG1-NOTCH1	(111)
Ma *et al*, 2016	EOC	EOC	*8p11.21*	486-5p	Down	*13q14.3*	OLFM4	(65)
Kobayashi *et al*, 2018	HGSOC	Advanced stages	*1p36.13*	1290	Up	-	Serum	(112)
Zhao, *et al*, 2015.	EOC	Complete response	*14q32.2*	136	Up	-	DNA repair and apoptosis	(69)
Zhao *et al*, 2014	EOC	Complete/poor response	*Xq25*	224-5p	Down	*3p21.1*	PRKCD	(113)
Wang *et al*, 2018	HGSOC	EOC	*6q13 13p.33*	30a-5p 200a-5p	Up	*6p21.2*	P21	(64)
Chen *et al*, 2016	EOC	Stage grade relapse	*17q23.1*	21	Up	*20q13.2*	HE4	(114)
Li *et al*, 2014	EOC	Stage III and IV	*11p15.5*	210	Up	*14q23.2*	HIF	(115)
Zhu *et al*, 2017	EOC	Resistance	*9p21.12*	204	Up	-	-	(116)
Fan *et al*, 2015	EOC	Poor prognosis stage III and IV tumor size metastasis	*17q21.32*	196a	Up	*21q22.12*	RUNX1	(117)

Table III. Continued.

First author/s, year	Ovarian carcinoma subtype	Associated with	*Locus* of the miRNA	microRNA	RNA regulation	*Locus* of the target	RNA from the locus target	(Refs.)
Koukorakis *et al*, 2018	HGSOC	HGSOC	*1p36.22* *1p36.33*	34a 200	Down Up	*9p24.1*	PD-L1	(118)
Liu *et al*, 2016	EOC	EOC	*8p22*	383	Up	*7q34*	Caspase-2	(119)
Dai *et al*, 2014	EOC	Stages III and IV relapse	*7q32.3*	29b	Down	*4q21.3*	MAPK10	(120)
Xiao *et al*, 2017	EOC	Therapy sensible poor prognosis	*19q13.41*	Let-7e	Down	*17q21.31* and *15q15.1*	BRCA1 and RAD51	(121)
Li *et al*, 2015	EOC	Therapy sensible poor prognosis metastasis	*1q22*	9	Down Up	*5q34 and 16q22.1*	CCNG1 and E-cadherin	(122)
Paudel *et al*, 2016	EOC	Stages III and IV	*22q11.21*	130b	Down	*1q36.11*	RUNX3	(123)
Duan *et al*, 2018	EOC	Poor prognosis	*3p21.2*	135a-3p	Down	*3p21.31*	CCR2	(124)
Chen *et al*, 2015	EOC	EOC	*5q32*	145	Down	*4q31.3*	TRIM2	(125)
Qin *et al*, 2015	EOC	Poor prognosis stages III and IV	*15q25.1*	184	Down	-	-	(126)
Liang *et al*, 2016	EOC	EOC	*1q41*	194	Up	*7q11.23*	PTPN12	(127)
Wei *et al*, 2017	EOC	EOC	*6p21.32*	219-5p	Down	*7p21.1*	Twist	(128)
Fu *et al*, 2016	EOC	Grades II and III poor prognosis	*Xp11.3*	222-3p	Down	*14q32.33 and 10q23.31*	AKT and PTEN	(129)
Wu *et al*, 2017	CCC	CCC		424	Down	*13q13.3*	DCLK1	(130)
Chen *et al*, 2015	EOC	Advanced stages Grades II and III	*Xq26.3*	490-3p	Down	*10q21.2*	CDK1	(106)
Zhang *et al*, 2016	EOC	Poor prognosis stage III and IV ascites lymph node metastasis grade III tumor size chemoresistance	*19q13.42*	520g	-	*15q22.31*	DAPK2	(131)
Zhang *et al*, 2016	EOC	Stage III and IV lymph node metastasis	*1p21.3*	137	Down	-	-	(132)
Liu *et al*, 2017	EOC	EOC	*11q13.4*	139	Down	*1q23.1*	HDGF	(133)
Xu *et al*, 2017	EOC	Stage III and IV tumor size lymph node metastasis	*9q32*	455	Down	*9q34.3*	NOTCH1	(134)
Yan *et al*, 2016	EOC	Age	*9q22.32*	23b	Down	*5q34*	CCNG1	(135)
Lin *et al*, 2015	EOC	Poor prognosis stages III and IV distant metastasis recurrence	*2q35*	26b	Down	*17q24.2*	KPNA2	(136)
Xu *et al*, 2017	EOC	EOC	*3q28*	28-5p	Up	*16q12.1*	N4BP1	(137)
Wang *et al*, 2017	HGSOC	Advanced stages	*11q21.1*	130a	Down	*9q34*	TSC1	(138)
Wang *et al*, 2016	EOC	Stages III and IV Grades II and III lymph node metastasis	*5q32*	143	Down	*6q23.2*	CTGF	(139)
Dong *et al*, 2015	EC	EC	*3p21.31*	191	Up	*9q21.33*	DAPK1	(140)
Niu *et al*, 2015	EOC	Stages III and IV High grade	*1q32.2*	205	Up	*10p11.22*	ZEB1	(141)

Table III. Continued.

First author/s, year	Ovarian carcinoma subtype	Associated with	*Locus* of the miRNA	microRNA	RNA regulation	*Locus* of the target	RNA from the locus target	(Refs.)
Dai *et al*, 2018	EOC	EOC	*6p12.2*	206	Down	*1p36.22*	mTOR	(142)
Xia *et al*, 2015	HGSOC, CCC	Tumors	*15q13.3*	211	Down	*11q13.3 and 7q21.2*	Cyclin D1 and CDK6	(143)
Wu *et al*, 2018	EOC	Poor prognosis death	*Xp11.3*	221-3p	Down	*3p14.3*	ARF4	(144)
Cao *et al*, 2018	EOC	Resistant	*Xq26.2*	363	Down	*20q13.3*	Snail	(145)
Xia *et al*, 2016	EOC	Stages III and IV Grades II and III	*8p22*	383	Down	*14q32.2*	YY1	(146)
Yuan *et al*, 2016; Li *et al* 2016	EOC	Stages III and IV Grades II and III lymph node metastasis	*14q32.31*	494	Down	*8q24.21 and 15q26.3*	c-Myc and IGF1R	(147,148)
Zhou *et al*, 2017	EOC	Stage III and IV Grade II and III distant metastasis	*7q36.3*	595	Down	-	-	(149)
Zhang *et al*, 2017	EOC	EOC	*15q24.1*	630	Up	*10p15.2*	KLF6	(150)
Shi *et al*, 2016	EOC	EOC	*1p32.3*	761	Down	*12q24.31*	MSI1	(151)
Xie *et al*, 2018	EOC	EOC	*Xp11.3*	221	Up	*15q15.1*	BMF	(152)
Wen *et al*, 2015	EOC	Stage III and IV Grade II and III lymph node metastasis	*17q25.3*	338-3p	Down	*6p21.1*	RUNX2	(153)
Salem *et al*, 2018	EOC	Grades II and III	*7q11.23*	590-3p	Up	*20p11.21*	FOXA2	(154)
Lin *et al*, 2016	EOC	EOC	*17p13.1*	497	Down	*10q24.31*	PAX2	(155)
Lin *et al*, 2018	EOC	Stage grade lymph node metastasis	*19q13.32*	330-5p	Up	*22q11.22*	MAPK	(156)
Chen *et al*, 2016	EOC	EOC	*12p13.31*	141	Down	*21q22.3*	SIK1	(157)
Zuberi *et al*, 2016	EOC	Stage lymph node metastasis	*19p13.2*	199a	Down	-	-	(158)
Agostini *et al*, 2018	MC	MC	*11q13.1 and 1q41*	192 and 215	Down	-	-	(78)
Guan *et al*, 2017	EOC	EOC	*19q13.42*	372	Down	*8q24.13, 13q12.11, 5q35.3, 10q21.1 and 13q13.3*	ATAD2, LATS2, P62, DKK1 and cyclinA1	(159)
Li *et al*, 2016	EOC	Advanced stages High grade lymph node metastasis	*2p16.1*	217	Down	*15q26.3*	IGF1R	(160)
Zhang *et al*, 2015	EOC	Poor prognosis	*4p15.33*	572	Up	*16p13.13 and 6p21.2*	SOCS1 and P21	(161)
Zhou *et al*, 2015	SOC	Preoperative	*6q13*	30a-5p	Up	-	-	(162)

EOC, epithelial ovarian cancer; HGSOC, high grade serous ovarian carcinoma; CCC, clear cells carcinoma; MC, mucinous carcinoma; EC, endometrioid carcinoma. High grade, grades II and III. Advanced stages, III and IV.

the tumor via cytoreduction, which involves extracting carcinoma cells from the patient. Chemotherapy is subsequently administered following cytoreduction in cases of advanced ovarian carcinoma. By contrast, radiation therapy uses

Table IV. Long non-coding RNAs expression associated to cancer functions derived from locus probed in specific ovarian carcinoma subtypes.

First author/s, year	Ovarian cancer subtype	Associated with	Locus	LncRNA	Regulation	(Refs.)
Xi *et al*, 2017	EOC	Poor prognosis stage grade lymph node metastasis	*5q11.2*	*lncBRM*	Up	(92)
Zhang *et al*, 2017	EOC	EOC	*1p21.2*	*NR_026689*	Up	(163)
Wang *et al*, 2017	EOC	Favorable prognosis stage Lymph node metastasis	*2q34*	*CPS1-IT1*	Down	(97)
Zhu *et al*, 2018	EOC	Metastasis CA-125 levels	*2p25.1*	*CTD2020K17.1*	Up	(164)
Qiu *et al*, 2017	EOC	EOC	*1q32.1*	*ElncRNA1*	Up	(165)
Gao *et al*, 2015	EOC	EOC	*10q23.1*	*HOST2*	Up	(166)
Wang *et al*, 2015	EOC	Poor prognosis Stage Histological grade Residual tumor Lymph node metastasis	*12q13.13*	*HOTAIR*	Up	(167)
Lu *et al*, 2018	HGSOC	Poor prognosis	*7p15.2*	*HOXA11-AS*	Up	(168)
Zhang *et al*, 2017	EOC	Poor prognostic stage lymph node metastasis	*2q31.1*	*HOXD-AS1*	Up	(93)
Du *et al*, 2018	EOC	Poor prognosis	*21q22.3*	*LINC00319*	Up	(169)
Shu *et al*, 2018	EOC	Poor prognosis stage grade lymph metastasis distant metastasis	9q21.31	*ARSR*	Up	(170)
Chen *et al*, 2017	EOC	EOC	*6p24.3*	*HULC*	Up	(171)
Liu *et al*, 2018	EOC	Stage tumor size distant metastasis	*6p21*	*LncSox4*	Up	(94)
Qunbo *et al*, 2018; Lin *et al*, 2018	EOC	Poor prognostic	*11q13.1*	*MALAT1*	Up	(172,173)
Yan *et al*, 2018	EOC	Poor prognostic stage depth of invasion lymph node metastasis distant metastasis	*2q31.1*	*MLK7-AS1*	Up	(95)
Yan *et al*, 2017	EOC	Favorable prognosis tumor size	*6p22.3*	*NBAT-1*	Down	(174)
Liu *et al*, 2018	EOC	Poor prognostic stage grade residual tumor metastasis	*11q13.1*	*NEAT1*	Up	(175)
Chen *et al*, 2018	EOC	Grade	*2q32.3*	*PCGEM1*	Up	(176)
Huang *et al*, 2018	EOC	Stage grade tumor size	1p13.2	*RP11-552M11.4*	Up	(177)
Li *et al*, 2017	EOC	Poor prognosis stage grade lymph node metastasis	*5q31.3*	*SPRY4-IT1*	Up	(178)
Zhu *et al*, 2017	EOC	Favorable prognosis stage grade lymph node metastasis CA-125 levels	*2q35*	*lncRNA-TUBA4B*	Down	(98)
Li *et al*, 2018	EOC	EOC poor prognosis stage grade tumor size	*22q12.2*	*lncRNA-TUG1*	Up	(179)
Hong *et al*, 2016	EOC	Poor prognostic stage lymph node metastasis chemotherapy response	*19p13.12*	*lncRNA-UCA1*	Up	(180,181)
Qiu *et al*, 2016	EOC	Poor prognosis stage grade	*9p21.3*	*ANRIL*	Up	(182)
Zhang *et al*, 2018	EOC	EOC	*10q26.11*	*CASC2*	Down	(90)
Cao *et al*, 2017	EOC	EOC	*8q24.21*	*CCAT1*	Up	(183)
Hua *et al*, 2018	EOC	EOC	*8q24.21*	*CCAT2*	Up	(184)

EOC, epithelial ovarian cancer; HGSOC, high-grade serous ovarian carcinoma.

high-energy particles to destroy tumor cells, either directly or indirectly, to inhibit further cell growth. Concomitantly, radiotherapy has been commonly used as a first-line treatment for ovarian carcinoma until the 1990s. It is now rarely used alone and is typically used with surgery (191). However, radiotherapy can still be beneficial in certain ways, such as reducing tumor size prior to surgery, treating areas where cancer has spread and providing palliative care (192,193). Ovarian carcinoma

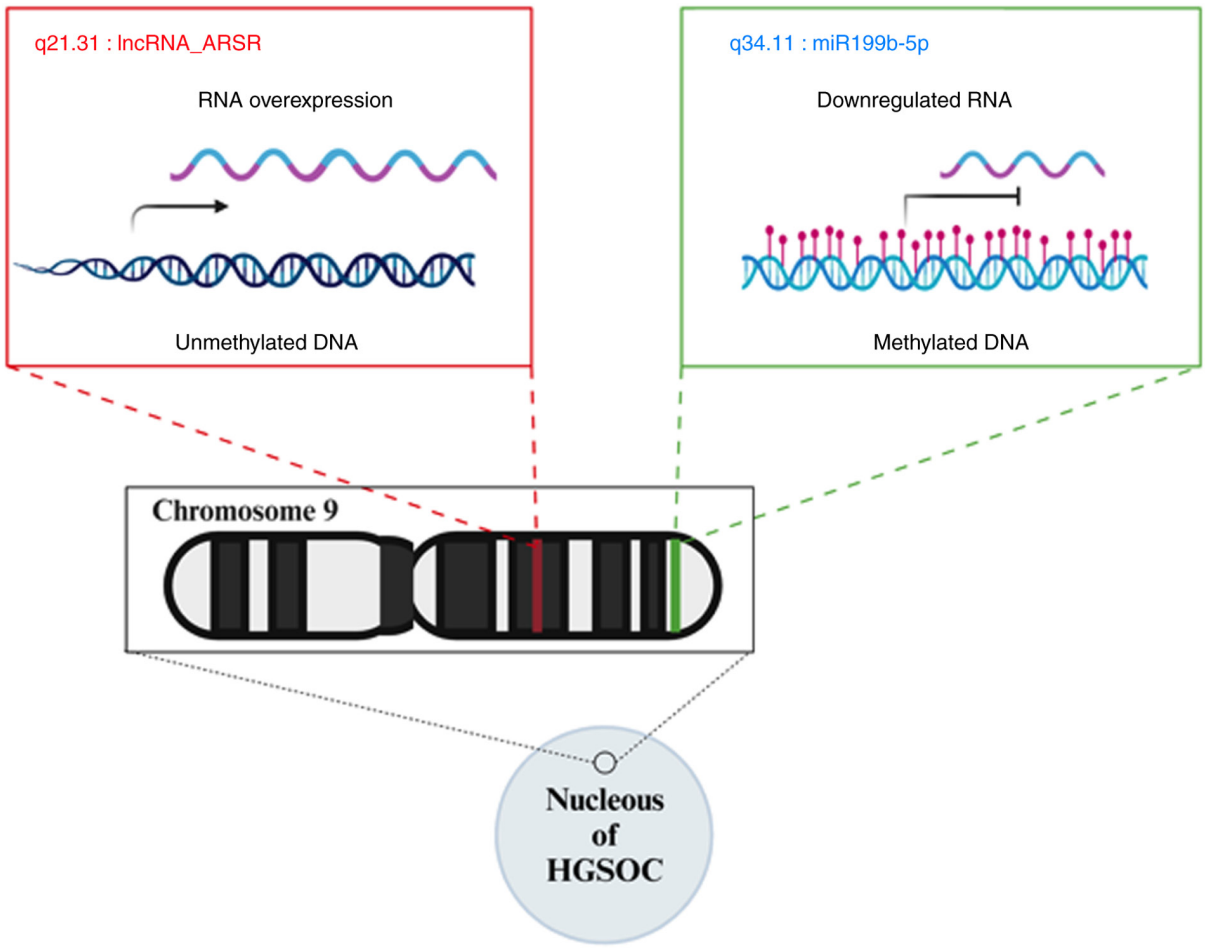

Figure 2. DNA methylation and RNA transcripts in the diagnosis and prognosis of ovarian carcinomas. Heterogeneous DNA methylation corresponds to heterogeneous ovarian carcinomas. RNA expression of the transcripts is associated with DNA methylation. Certain studies have characterized DNA methylation and RNA transcription of specific genes in ovarian carcinoma subtypes. Generally, with a few exceptions, different RNAs are affected by the methylation status of the DNA. For example, molecular diagnosis of HGSOC is performed by chromosome 9 *locus* Chr9q21.31 that contains unmethylated DNA; an overexpression of the large non-coding RNA *ARSR* is noted. By contrast, in the locus Chr9q34.11, which contains a methylated DNA, downregulation of miR199b-59p expression is noted. Created by BioRender.com. Accessed on 09/2024. HGSOC, high-grade serous ovarian carcinoma subtype; miR, microRNA.

cells are radiosensitive at the early stages of development (194), notably in low-grade carcinoma subtypes such as EC (195).

In contrast to these observations, ovarian carcinomas at the late stages are resistant to both radiotherapy and chemotherapy. This resistance is often associated with p53 mutation and CIN (192,196). It is notable that radiotherapy increases global unmethylated DNA levels in cancer cells, while hypomethylated DNA is linked to increased sensitivity to radiotherapy. This explains the ability of DNA methylation inhibitors (such as decitabine) to sensitize ovarian carcinoma cells to radiotherapy (197). By contrast, RNA transcripts can increase resistance to radiotherapy treatment, such as Snail, Slug, NOX4, miR200, miR-299 and MTDH. Conversely, reducing the levels of specific RNA transcripts in ovarian carcinoma cells can increase the sensitivity of the tumor cells to radiotherapy (198-202).

Chemotherapy presents a challenging environment for cells, aiming to eliminate tumor cells and improve the prognosis for patients with cancer. The standard chemotherapy treatment for ovarian carcinoma combines carboplatin and paclitaxel. Chemotherapy can alter the nuclear structure, DNA methylation and RNA expression in ovarian carcinoma cells (203-205). To date, the association of methylation with the incidence of cancer in patients is not directly known. However, DNA methylation is associated with chromosomal instability of high-grade serous ovarian carcinoma. This is the most aggressive subtype of ovarian cancer. It can be inferred that by understanding the relationship between methylation and CIN, the progression of ovarian cancer can be predicted. For example, it is known that the HGSOC subtype with *TP53* mutation and CIN is associated with DNA hypermethylation in patients with poorer prognosis (206-213). HGSOC is characterized by *TP53* mutation and CIN and is linked to chemotherapy resistance; it is also considered to be the more resistant and heterogeneous subtype of ovarian carcinomas (214). For example, treatment with paclitaxel in specific cell line models induces overexpression of mdr1 and the lncRNAs UCA1 and long intergenic non-coding RNA *linc00312* (215).

Paclitaxel is a drug that inhibits depolymerization of microtubules. It arrests cells in the G_2/M phase. It also induces CIN, leading to cell death. However, certain ovarian carcinoma cells are resistant to paclitaxel. Certain miR biomarkers, such as miR-134 and miR-224-5p, are associated with EOC resistance to paclitaxel chemotherapy with 85 and 90% sensitivity, respectively (94,102). Studies in ovarian carcinoma have shown that RNA transcript levels are altered during paclitaxel treatment

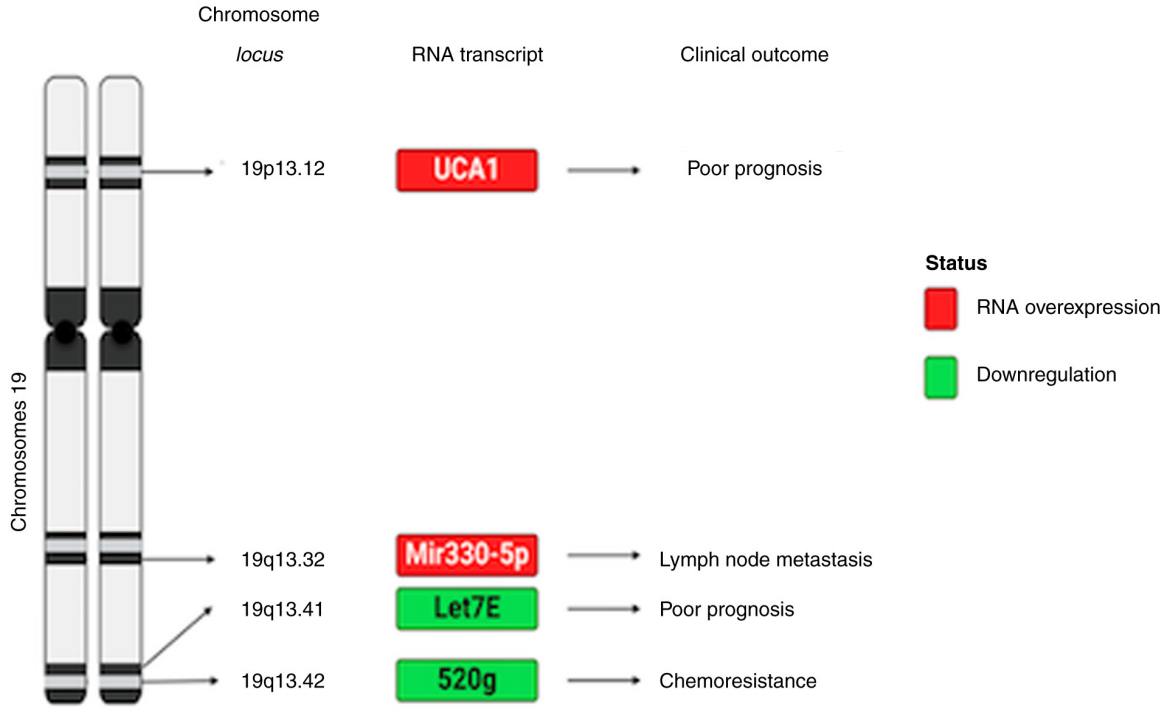

Figure 3. The variability of ncRNAs is related to clinical pathogenesis and resistance in ovarian carcinoma. The differential expression status between ovarian cancer and normal tissue has been associated with clinical outcomes such as ovarian carcinoma subtype, progression, metastases, radioresistance and chemoresistance, and more importantly, in the disease prognosis of the patients. For example, the ncRNA expression levels of the ovarian carcinoma type indicated that the aforementioned genes were located in a specific locus from a unit of chromosome 19. Overexpression of *UCA1*, a large non-coding RNA located in *locus* 19p13.12 and downregulation of the *Let7E* miR levels located in 19q13.41 were associated with poor prognosis. Similarly, overexpression of miR330-5p in 19q13.32 was associated with lymph node invasion and downregulation of miR520g levels was associated with resistance to chemotherapy. ncRNAs overexpressed are shown in red and the downregulated RNA transcript are shown in green. ncRNA, non-coding RNA; miR, microRNA.

in ovarian cancer cells. For example, treatment of A2780, OVCAR3, SKOV3, and SW626 cells with paclitaxel induces overexpression of *mdr1* (215), *UCA1* and *lincRNA00312*.

Previous studies have shown that cisplatin increases the expression of *ZEB1* and *MP63* (216,217). It is notable that the use of array expression and PCR validation in the A2780 cisplatin-resistant cell line revealed that the expression levels of the following six miRs were upregulated: miR-1064, miR-300, miR-193b, miR-642 and miR-1299; however, the expression levels of the following five miRs were downregulated: miR-625, miR-20b, miRPlus-F1147, let-7c, miR-1231 and miR-542-3p (214,215,218,219). This evidence suggests that RNA transcripts are differentially expressed in chemotherapy-resistant cells compared with sensitive cells, providing a solid basis for further research. It also indicates the implications for the survival outcomes of the patients with ovarian cancer (220-225) (Fig. 3).

3. Discussion and conclusions

Ovarian carcinoma is a type of cancer resulting from tissue transformation and can occur both in hereditary (20%) and sporadic (80%) forms. DNA methylations repress RNA transcription differentially in ovarian carcinoma subtypes. This suggests that DNA methylation of ovarian carcinoma subtypes is more similar to their tissue of origin with regard to their nuclear characteristics. Ovarian carcinoma presents a complex molecular landscape where DNA methylation and RNA expression play crucial roles in the disease development, progression and treatment response. DNA methylation serves as both an early event in carcinogenesis and a key regulator of gene expression, either silencing or activating RNA transcription based on the methylation status of specific loci.

The characteristics of nuclear vestiges vary in a directional range of RNA transcripts. In addition, the directional way of variation of the RNA transcripts is directed by FIGO stages observed in every carcinoma subtype. The molecular ovarian carcinoma subtypes are five and can be classified as follows: High-grade serous, low-grade serous, endometrioid, mucinous and clear cell; however, there are other subtypes to be described since they belong in the five subtypes or other similar subtypes, such as carcinosarcoma (analogous to malignant mixed Mullerian/mesodermal tumors) and malignant Brenner tumors. Other cellular subtypes are currently in discovery. This is particularly relevant in HGSOC, where distinct methylation patterns have been identified, linking them to tumor origin, subtype differentiation and patient prognosis. The heterogeneity of ovarian carcinoma is further exemplified by the differential expression of miRs and lncRNAs, which are involved in gene regulation.

The molecular prognosis of ovarian carcinoma varies. Firstly, hereditary ovarian carcinoma exhibits a greater effect than sporadic ovarian carcinoma. By contrast, the survival of each patient with spontaneous ovarian carcinoma depends on the carcinoma development and the subtype. At a molecular level, deviations in the DNA methylation and RNA transcription have been associated with metastasis stages and the development of therapy-resistant cancer cells. These findings suggest that molecular signatures, including miR and lncRNA profiles, could

serve as valuable biomarkers for diagnosis, prognosis and therapeutic targeting in ovarian carcinomas. Despite the advances in the understanding of the molecular underpinnings of ovarian carcinomas, the disease prognosis for patients, notably those diagnosed with advanced-stage or metastatic disease remains poor, with survival rates being markedly lower among these groups.

Current diagnostic and therapeutic strategies are increasingly incorporating molecular data, including RNA transcriptomics and DNA methylation analysis, to improve the precision of treatment approaches. While hereditary mutations, such as those noted in *BRCA1/2*, confer a significant risk, epigenetic changes, notably in the later stages of the disease, are critical in shaping the tumor phenotype and response to therapy. In clinical practice, evidence leads to the hypothesis that certain genes could be used as a combination to adjust cancer treatments. However, a pair of primers may not provide a clinical solution. Therefore, practical techniques, such as PCR and sequencing, are used for validation of the next biological characterization of chromosomes. In the present review, it was hypothesized that chromosome instability, which is characterized by gain of chromosomes in cancer cells and the loss of specific chromosomes or their translocation, should be the focus of future research. For example, changes in DNA methylation of chromosomes 9 and 19 (Figs. 2 and 3) in high-grade serous ovarian carcinoma are associated with ovarian carcinoma progression and resistance to treatments.

Ultimately, a comprehensive understanding of the molecular heterogeneity in ovarian carcinoma, including the roles of DNA methylation and RNA transcription into the nucleus, is essential to develop a vision for more effective treatments, increase the understanding of disease progression and improve long-term outcomes for patients. The continued exploration of these molecular pathways holds the potential not only to revolutionize but also to reform the clinical management of ovarian carcinomas.

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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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