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ORIGINAL ARTICLE

CDK9 and SMYD3 are Diagnostic, Prognostic Markers and Probable Therapeutic Targets in Serous Ovarian Carcinomas

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ABSTRACT

Background: The basis of cancer management is understanding its underlying molecular abnormalities. To improve the survival of ovarian cancer patients, new therapeutic targets and prognostic markers are needed. SMYD3 and CDK9 are two markers that play an important role in epigenetic regulation and promotion of the oncogenic process. They have to be under investigation to be used as targets for therapy. This study aims at evaluating the diagnostic and prognostic value of the immunohistochemical expression of SMYD3 and CDK9 in serous ovarian carcinoma (SOC).

Methods: 50 cases of SOC and 50 benign ovarian lesions cases were included in this study. The morphological classification was assessed according to the World Health Organization criteria. Immunohistochemistry (IHC) for CDK9 and SMYD3 was performed.

Results: SMYD3 and CDK9 was highly expressed in cancer compared with benign lesions ($p < 0.001$ and < 0.05 respectively). High CDK9 and SMYD3 expression were significantly associated with vascular invasion and advanced stage disease ($p < 0.001$ for both). Patients who exhibited high SMYD3 and CKD9 expression showed poor treatment response, drug resistance and higher frequency of relapse and mortality.

Conclusion: The immunohistochemical staining of SMYD3 and CDK9 is higher in serous ovarian carcinoma compared with benign ovarian lesions and represents a worse prognostic factor.

Keywords: SMYD3, CDK9, serous ovarian carcinomas, prognosis, immunohistochemistry.

INTRODUCTION

Because of the high incidence of relapse after usual treatment modalities, ovarian cancer is the most lethal gynecological tumor and is considered one of the major health problems in females [1]. That is why identifying new markers suspected to have a role in the occurrence of drug resistance and may be a target for therapy is a high priority. SET and MYND domain-containing protein 3 (SMYD3) is also a gene transcriptional regulator. It is a lysine methyltransferase, which methylates lysines on histone and the non-histone proteins. Its level increases in different types of cancer. It can occupy binding motifs on target gene promoters and regulate

target gene expression by methylating histones such as H3K4 and H4K5 in the nucleus [2]. In addition, SMYD3 induces VEGF1 methylation with stimulation of downstream signaling [3]

Cyclin-dependent kinases (CDKs) are protein kinases that are implicated in the progression of the cell cycle and DNA transcription [4]. Palbociclib, a dual CDK4/6 inhibitor was approved by the Food and Drug Administration as a first-line treatment for estrogen receptor-positive and HER 2-negative breast cancer [5]. Cyclin-dependent protein kinase 9 (CDK9) is a regulator of transcription that is involved in the oncogenic transformation of many types of human cancer, including leukemia, cervical cancer, prostate cancer, glioblastoma, breast cancer, melanoma, and lung cancer [6].

Downregulating SMYD3 induces BIRC3 expression reduction, and this induces cell apoptosis [3]. Moreover, SMYD3 is a cofactor for ERα that promotes its effectiveness, and it can interact with ER in the ligand binding domain with subsequent activation of the transcriptional genes [7]. These findings indicate that SMYD3 will be a hopeful target for therapy for cancer and a promising therapeutic agent for ovarian cancer [3].

In this study, we aimed to investigate CDK9 and SMYD3 expression in ovarian cancer and detect their association with different clinicopathological diameters in these patients.

METHODS

Fifty cases of SOCs and fifty cases of benign serous cystadenoma were involved in this study. Archival paraffin-embedded blocks and their complementary clinical files for this retrospective cohort study we retrieved from pathology department of faculty of medicine. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans and it was approved by the Institutional Research Board by number (ZU-IRB # 9760).

All patients did not receive preoperative chemotherapy. Cases were diagnosed and treated at the Zagazig University Hospital, from 2015 to 2019 and were followed-up in the Clinical and Medical Oncology Departments until 2022.

Staging done according to FIGO recommendations [8]. Exclusion criteria were secondary recurrent tumor, insufficient sample, other histological subtypes, and incomplete clinical data.

Post-operative chemotherapy regimens that consisted of carboplatin-paclitaxel, carboplatin- gemcitabine, and ifosfamide-mesna-etoposide were given to patients. Time was calculated by months concerning the PFS and OS, from the time of first diagnosis to the last follow-up visit, recurrence, or any cause of death [9]. Patients were examined clinically and radiologically in line with obtaining a complete history. Patients underwent either optimal or suboptimal surgical resection, while debulking was complete or incomplete and biopsy through exploration.

Immunohistochemistry (IHC)

Sections for IHC undergo deparaffinization then the endogenous peroxidase activity blocked with 0.3% hydrogen peroxide. The sections were then microwaved in 10 mM citrate buffer (pH 6.0) to expose the epitopes. The slides were incubated with primary rabbit monoclonal antibodies, against CDK9 (2316 S, 1:300 dilution, pH 9.0, Cell Signaling Technology) and anti-SMYD3 antibody (ab 187149, 1:100, abcam).

Evaluation of the immunohistochemical reactions:

The considerable expression of CDK9 is nuclear, and it was evaluated separately by 2 independent pathologists according to the percentage of cells with positive staining of the tumor cell nuclei. Expression of CDK9 were graded into 5 groups: group 1+ when < 10% of the cells stained positive; 2+ if 10–25% of cells stained positive; 3+, 26–50% positive cells; 4+, 51–75% positive cells; and 5+ if more than 75% of cells showed positive nuclear staining. Scores 3,4 and 5 considered high expression while 1 and 2 considered low [10].

According to the net score of multiplying intensity and percentage, SMYD3 staining was evaluated. Staining intensity was graded from 1 to 3 (1, negative; 2, moderate; 3, strong). The percentage of SMYD3-positive cells was also scored at levels 1 to 4 (0–10%, 11–25%,26–75%, 76–100%). A score ranging from 1 to 12 obtained, low expression level considered when the score is up to 4 and it is high if the score is > 4 [11].

Statistical analysis:

Data analysis was performed using the software SPSS version 20. Means and standard deviations are used to describe quantitative variables while absolute frequencies are used for categorical variables. The chi-square test and Fisher exact test were used to compare the different variables when appropriate. For comparing two groups regarding ordinal categorical data, chi-square for the trend test was used. The Phi correlation coefficient was used to assess the strength and direction of association between two dichotomous categorical variables. Survival analysis and Kaplan Meire plot were used to measure the fraction of subjects living for a certain amount of time after treatment and for analyzing the expected duration of time until one event occurs, either death or recurrence. The level of statistical significance was set at 5% (P<0.05).

RESULTS

Patient characteristics:

A resume of the clinicopathologic parameters of the studied 50 cases of ovarian cancer is presented in table 1 and figure 1. Concerning the difference between benign and malignant groups regarding SMYD3 and CDK9 expression (table 2), the difference was statistically significant (significantly higher in malignant group).

SMYD3 and CDK9 expression and their clinico-pathological associations (table 3 & figure 2).

There is a statistically significant relation between SMYD3 expression and all stages, vascular, neural, distant metastasis, treatment response, ascites, relapse, and death. Those with high expression had higher stage, vascular, neural invasion, and distant metastasis, non-optimized surgery, higher incidence of ascites, poor treatment response and resistance, and higher frequency of relapse and mortality. There is a statistically significant relation between CDK9 expression and all of tumor size, grade, stage, vascular, neural, lymph invasion, distant metastasis, ascites, relapse, and death. Those with high expression had stage, vascular, lymph, neural invasion and distant metastasis, non-optimized surgery, higher incidence of ascites, higher frequency of relapse and mortality.

Correlation between SMYD3 and CDK9 among the studied cancer patients (table 4), There is a significant positive correlation between all SMYD3 and CDK9 among the studied patients.

Relation between survival (disease free & overall) and marker expression (table 5&6, figure 3):

The Mean DFS and OS were 17.61 ±1.95, 18.14 ± 2.04 respectively at 95% CI (13.78 – 21.44, 14.13 – 22.14 months)respectively for patients with high SMYD3 expression which were shorter than the mean DFS and OS for patients with low SMYD3 expressions with significance p=<0.001.The mean DFS and OS were 16.56 ±1.95, 16.65 ±1.96 respectively at 95% CI were 12.75-20.38, 28.21 – 32.41 months respectively for patients with high CKD9 expression which were shorter than patients with lower CDK9 with significance p=0.001.

Elevated expression of SMYD3 and CDK9 showed a statistically significant association with survival parameters (disease free & overall). All those with high expression of any marker had significantly lower OS. All those with positive expression of any marker had significantly lower DFS.

Table 1: Clinicopathological data of the studied patients

Clinical features	Total N=50 (%)	Clinical features	Total N=50 (%)
Age group: ≤50 years >50 years	 20(40%) 30(60%)	PT: I II III	 24 (48%) 14 (28%) 12 (24%)
Size: ≤12 cm >12 cm	 26 (52%) 24 (48%)	Stage: Ia Ib Ic II III IV	 7 (14%) 11 (22%) 1 (2.0%) 7 (14%) 20 (40%) 4 (8%)
Grade: High grade Low grade	 29 (58%) 21 (42%)	Ascites: Absent Present	 18 (36%) 32 (64%)
Vascular invasion: Negative Positive	 31(62%) 19(38%)	Surgical excision: Non-optimized Optimized	 30 (60%) 20 (40%)
Neural invasion: Negative Positive	 31(62%) 19(38%)	Treatment response: CR PD PR SD	 6 (20%) 16 (53.3%) 3 (10%) 5 (16.7%)
LN invasion: Negative Positive	 35(70%) 15(30%)	Relapse: Negative Positive	 24 (56%) 22 (44%)
Distant metastasis: Negative Positive	 31(62%) 19(38%)	Mortality: Negative Positive	 27 (54%) 23 (46%)

Table 2: Comparison between the studied groups with benign and malignant tumors regarding age, tumor size and marker expression

	Nature		Test	
	Malignant N=50(%)	Benign N=50 (%)	$\chi2$	p
SMYD3: Low High	 28 (56%) 22(44%)	 46 (92%) 4 (8%)	16.84	<0.001*
CDK9: Low High	 30 (60%) 20 (40%)	 40 (80%) 10 (10%)	4.761	<0.05

t independent sample t test chi square test *p below 0.05 is statistically significant

Table 3: Relation between SMYD3, and CDK9 expression and clinic-pathological features of the studied patients

Clinical features	Total N=50 (%)	SMYD3		P	CDK9		p
		SMYD3 high 22 (44%)	SMYD3 Low 28(56%)		High (-)ve 20 (40%)	Low (+)ve 30 (60%)	
Grade: High grade Low grade	 29 (58%) 21 (42%)	 13 (48.1%) 9 (39.1%)	 16 (51.9%) 12 (60.9%)	0.522	 14 (59.1%) 6 (26.1%)	 13 (40.9%) 17 (73.9%)	0.064
Vascular invasion: Negative Positive	 31(62%) 19(38%)	 6 (19.4%) 16(84.2%)	 25 (80.6%) 3 (15.8%)	0.001*	 3 (9.7%) 17(89.5%)	 28(90.3%) 2 (10.5%)	<0.001*
LN invasion: Negative Positive	 35(70%) 15(30%)	 13 (37.1%) 9(60%)	 22 (62.9%) 6 (40%)	0.136	 11 (31.4%) 9 (60%)	 24 (68.6%) 6 (40%)	0.059

Clinical features	Total N=50 (%)	SMYD3		P	CDK9		p
		SMYD3 high 22 (44%)	SMYD3 Low 28(56%)		High (-)ve 20 (40%)	Low (+)ve 30 (60%)	
Distant metastasis:							
Negative	31(62%)	6 (19.4%)	25 (80.6%)	<0.001*	3 (9.3%)	28 (90.7%)	<0.001*
Positive	19(38%)	16 (84.2%)	3 (15.8%)		17 (89.5%)	3 (10.3%)	
PT:							
I	24 (48%)	10 (41.7%)	14 (58.3%)		6 (25%)	18 (75%)	
II	14 (28%)	7 (50%)	7 (50%)	0.923¥	8 (57.1%)	6 (42.9%)	0.092¥
III	12 (24%)	5 (41.7%)	7 (58.3%)		6 (50%)	6 (50%)	
Stage:							
Ia	7 (14%)	0(0%)	7(100.0%)		0(0%)	7 (100%)	
Ib	11 (22%)	1 (9.1%)	10 (90.9%)	0.001*¥	0(0%)	11(100%)	<0.001*¥
Ic	1 (2.0%)	1 (100%)	0 (0%)		0(0%)	1(100%)	
II	7 (14%)	1(14.3%)	6 (85.7%)		0(0%)	7 (100%)	
III	20 (40%)	15 (75%%)	5 (25%)		16 (80%)	4 (20%)	
IV	4 (8%)	4 (100%)	0 (0%)		4(100%)	0 (0%)	
Ascites:							
Absent	18 (36%)	1 (5.6%)	17 (94.4%)	<0.001*	0 (0%)	18(100%)	<0.001*
Present	32 (64%)	21(65.6%)	11 (34.4%)		20 (62.5%)	12(37.5%)	
Treatment response:							
CR	6 (20%)	0 (0%)	6 (100.0%)		0 (0%)	6 (100%)	
PD	16 (53.3%)	16 (100%)	0 (0.0%)	<0.001*¥	15 (93.8%)	1 (6.2%)	0.184¥
PR	3 (10%)	0 (0%)	3 (100.0%)		2 (66.7%)	1 (33.3%)	
SD	5 (16.7%)	3 (60.0%)	2 (40.0%)		3 (60%)	2 (40%)	
Relapse:							
Negative	24 (56%)	1 (4.2%)	23 (95.8%)	<0.001*	0(0%)	24(100%)	<0.001*
Positive	22 (44%)	17 (77.3%)	5 (22.7%)		16(72.7%)	6(27.3%)	
Mortality:							
Negative	27 (54%)	3 (11.1%)	24 (88.9%)	<0.001*	0 (0%)	27(100%)	<0.001*
Positive	23 (46%)	19 (82.6%)	4 (17.4%)		20 (87%)	3(13%)	

P for chi square test *p less than 0.05 is statistically significant ¥ chi square for trend test

Table 4: SMYD3 Correlation with CDK9 among the studied patients

	SMYD3	
	Phi	**p**
CDK9	0.674	<0.001*

rs: Spearman's correlation.

Table 5: Relation between disease free survival and marker expression

		Total N	N of Events	Censored		Survival time, Months		P
				N	%	Mean		
						Estimate ±SD	95% CI	
SMYD 3	Low	28	5	23	82.1%	34.46 ± 0.76	32.98 – 35.94	<0.001*
	High	18	17	1	5.6%	17.61 ±1.95	13.78 – 21.44	
CDK9	Low	30	6	24	80.0%	33.9 ± 0.91	32.11-35.69	0.001*
	High	16	16	0	0.0%	16.56 ±1.95	12.75-20.38	
Overall		46	22	24	52.2%	27.87 ± 1.51	24.92 – 30.82	

*p less than 0.05 is statistically significant

Table 6: Relation between overall survival and marker expression

		Total N	N of Events	Censored		Survival time, Months		P
				N	%	Mean		
						Estimate ±SD	95% CI	
SMYD3	Low	28	4	24	85.7%	34.93 ± 0.64	33.69 – 36.17	<0.001*
	High	22	19	3	13.6 %	18.14 ± 2.04	14.13 – 22.14	
CDK9	Low	30	3	27	90.0%	34.8 ± 0.66	35.3 – 36.22	0.001*
	High	20	20	0	0.0%	16.65 ±1.96	28.21 – 32.41	
Overall		50	23	27	54.0%	27.54 ± 1.53	24.55 – 30.53	

*p less than 0.05 is statistically significant

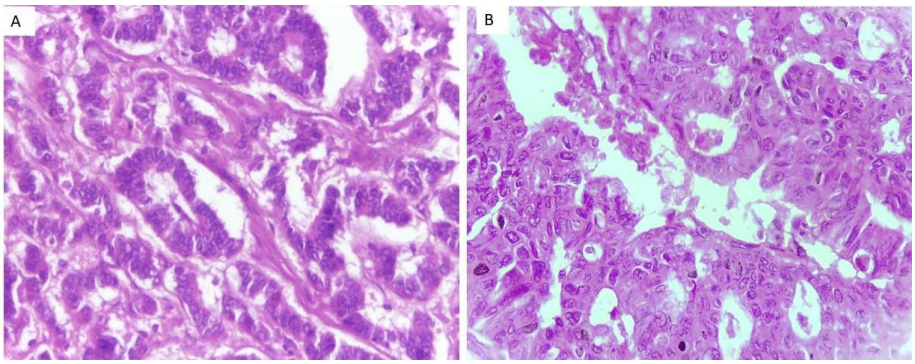

Figure (1): Histological features of serous ovarian cancer (SOC). A) low grade SOC, cells with mild pleomorphism and mild nuclear atypia, mitosis is infrequent (H&E x400). B) high grade SOC, cells are pleomorphic with marked nuclear atypia and frequent mitosis (H&E x400).

APPENDIX

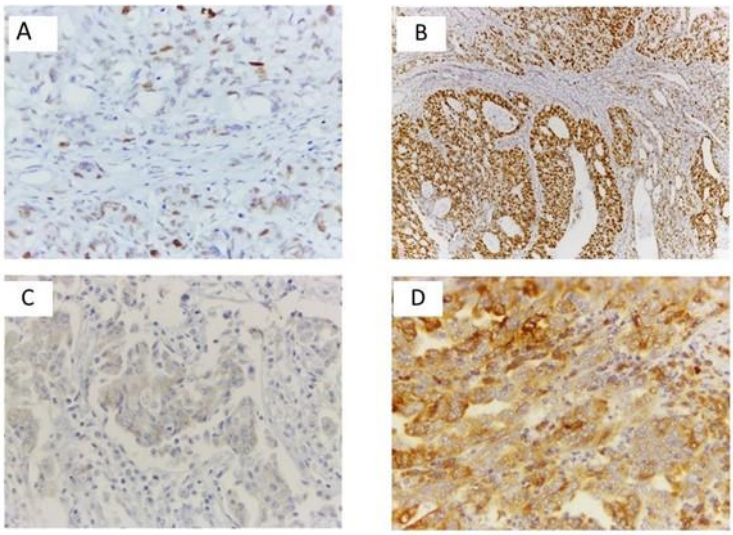

Figure (2): Immunohistochemical analysis of CDK9 and SMYD3 expression in epithelial ovarian cancer (EOC). A) low nuclear expression of CDK9 in a case of EOC (x400). B) show high nuclear expression of CDK9 (x200). , C) low expression of SMYD3 in a case of EOC (x400)..D) high SMYD3 expression in a case of EOC (x400).

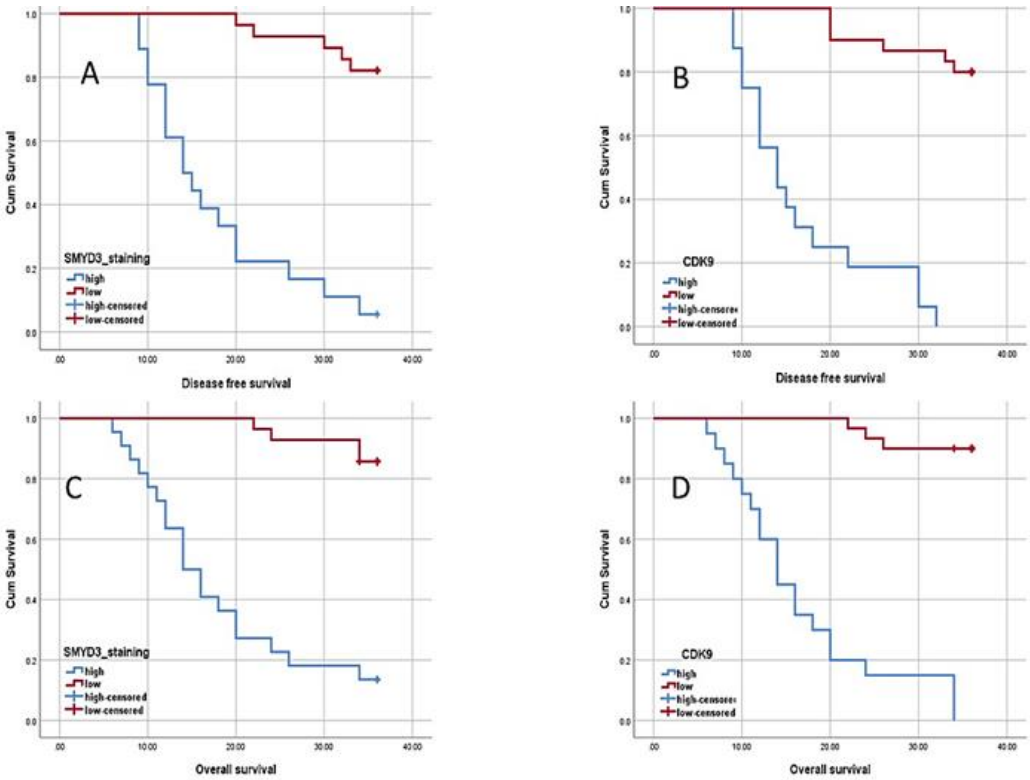

Figure (3): Kaplan Meier plot showing relation between (A) disease free survival and SMYD3 expression among studied patient (B) disease free survival and CDK9 expression among studied patients (C) overall survival and SMYD3 expression among studied patients (D) between overall survival and CDK9 expression among studied patients.

DISCUSSION

Ovarian cancer is often diagnosed at an advanced stage, and most cases develop recurrence within 5 years, even after cytoreduction followed by platinum-paclitaxel chemotherapy [12]. Research must focus on identification of new markers that can predict the response to therapy or offer alternative strategies of therapy.

Both SMYD3 and CDK9 are promising therapeutic targets; therefore, we investigated their occurrence in ovarian cancer and their relationship to the clinicopathological diameters. Cancer occurrence and progression are based on epigenetic DNA modifications that can be modified by external agents and can be reversed [13]. Histone modification, which is the mechanism of SMYD3 action, is one of these epigenetic changes that become a target for recent therapies [14]. With the development of SMYD3 inhibitors, the identification of cancer that expresses SMYD3 and can benefit from this therapy is needed [15].

In line with Jiang et al., [3] in this work ovarian cancer tissues revealed higher SMYD3 expression than its expression in benign ovarian epithelial lesion indicating that SMYD3 has a vital role in ovarian tissue malignant transformation.

A significant association between high SMYD3 expression and advanced stages was detected. This may be attributed to its role in p53 (the genome guardian) downregulation with subsequent interference with the regulatory mechanisms of the cell cycle [16]. That is why SMYD3 is called by some authors as a cancer genome keeper [17].

In this work, a significant association between the expression of SMYD3 and malignant ascites was detected. This is reasonable as it affects the level of E-cadherin and vimentin with a consequent role on (epithelial-mesenchymal transition) EMT (16). SMYD3 also potentiates angiogenesis by

methylating activation of vascular endothelial growth factor receptor 1 [15], which is one of the key factors in ascites formation [17].

In agreement with the current results, Zhang et al (2019), stated that SMYD3 was increased in ovarian carcinoma and correlated with tumor metastasis and poor clinical outcome. Rajput et al., revealed that inhibition of CDK9 restores tumor suppressor gene action with subsequent decrease in cell multiplication. Moreover, its inhibition suppresses cell proliferation with apoptosis induction in breast cancer [18]. In line with Li et al [19] the current work revealed a significantly higher CDK9 expression in ovarian cancer compared to that in benign ovarian tumor specimen.

In agreement with Wang et al. and Parvathareddy et al [12] a significant association between CDK9 and stage, and metastasis in this work was detected. This finding indicates that using inhibitors of CDK9 in ovarian cancer may be valuable in the limitation of disease especially if diagnosed in the early stage giving hope for changing the prognosis and the nature of this aggressive disease to be a curable one.

Furthermore, Wang et al [10] evaluated the CDK9 expression in metastatic and recurrent ovarian cancer tumor tissues and detected a higher expression compared with patient-matched primary tumor samples.

Elevated CDK9 protein level was significantly correlated with poor patient survival in this work. Wang et al [10] reported that patients with low CDK9 expression had significantly better prognostic measures in both DFS and OS and this completely agree with our results.

We observed poor survival for patients who exhibited over expressed CDK9 in agreement of Parvathareddy et al [12] who reported that CDK9 over-expression was significantly associated with poor recurrence-free survival and resistance to initial platinum-paclitaxel chemotherapy.

As far as we know, no previous work investigated the relation between SMYD3 and CDK9. In this work, a significant correlation was detected between SMYD3 and CDK9 expression ($p < 0.001$). This finding is reasonable, as Jiang et al [3] found that SMYD3 knockdown induces the upregulation of the inhibitors of cyclin-dependent kinase as p16. Moreover, according to Lv et al findings, the use of chromatin immunoprecipitation confirms that SMYD3's transcriptionally regulates the cyclin-dependent kinase 2 promoter regions [20].

CONCLUSION

In conclusion, our results showed that SMYD3 and CDK9 expression significantly associated with poor prognostic diameters in serous ovarian carcinoma. Their overexpression can also identify a group of patients with increased susceptibility to recurrence across the patient cohort and help in selection of those who may benefit from additional alternative therapies targeting SMYD3 or CKD9.

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