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Short Review

Immunohistochemical expression of p53 and Fox A1 in epithelial ovarian cancer

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Abstract

Background: Ovarian cancer (OC) is the fifth cause of cancer mortality in females. There were an estimated 300,000 new cases of OC diagnosed worldwide in 2018, corresponding to 3.4% of all cancer cases among women. The high mortality rate of OC attributed to asymptomatic growth of the tumor leads to its diagnosis at advanced stages. About 85% - 90% of OC are epithelial including serous, endometrioid, clear cell, and mucinous carcinoma.

Aim: To study the immunohistochemical (IHC) expression of FOX A1 and p53 in epithelial OC and its association with prognostic indicators such as age, tumor size, stage, grade, and histological type.

Materials and methods: The study included 52 cases with EOC from the pathology department, faculty of medicine, Aswan, and Sohag Universities, in the period from January 2017 to December 2019. This study involved 52 patients with OC and a median age of 53 years. Different histological types were included as 37 serous, 12 mucinous, 1 case endometroid 2 cases clear cell OC. The study cases were classified into 22 Grade I, 16 Grade II, and 20 Grade III. About 22 cases were at stage I, 9 at stage II, 11 at stage III, and 10 at stage IV. Tissue sections were stained using the IHC technique with FOX A1 at a dilution of 1:100 and p53 at 1:100.

Results: A statistically significant correlation was found between FOX A1 expression and advanced patient's age, high grade, advanced stage, ruptured capsule, and ascites, regardless of tumor laterality. No significant association was found between p53 immunoexpression and the same clinic-pathological parameters although p53 was associated with serious type.

Conclusion: FOXA1 immunoexpression in EOC is considered a poor prognostic factor in EOC. FOX A1 could be a potential therapeutic target and prognostic marker in EOC.

More Information

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Keywords: Ovarian cancer; FOX A1; P53; Prognostic marker; Immunohistochemistry (IHC)

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Introduction

Ovarian cancer (OC) ranks as the fifth leading cause of malignancy-associated mortality in females. There were an estimated 300,000 new cases of ovarian cancer diagnosed worldwide in 2018, corresponding to 3.4% of all cancer cases among women. Although there is substantial geographic variation in the burden of ovarian cancer (rates varying from 5.0 per 100,000 person-years in Africa to 9.5 per 100,000 person/year in Europe). The high mortality rate of OC is attributed to asymptomatic growth of the tumor, delayed onset of symptoms, and lack of proper screening which leads to its diagnosis in the advanced stages. That is why it is called silent killer [1].

Studies showed that up to 90% of all OC have an epithelial origin and the remaining OC are non-epithelial. In all epithelial ovarian cancers (EOCs), 3% are mucinous. There are several histologic types of epithelial ovarian cancer, involving serous, endometrioid, clear cell, mucinous, transitional, and undifferentiated carcinomas [2].

Fork headbox (FOX) A1 represented a potential candidate gene for therapeutic targeting in human EOC; FOXA1 is a transcription factor that is expressed widely and functions in the development of multiple types of human tissue. FOXA1 served a major function in modulating nuclear steroid receptor activity in breast and prostate cancer, and it was suggested that FOXA1 may be associated with pro-tumorigenic phenotypes. FOXA1 is over-expressed in EOC and associated with clinicopathological features, involving overall survival time. FOXA1 potentially represents a novel biomarker and therapeutic target for EOC [3].

P53 is a tumor suppressor protein that regulates the expression of different genes included in apoptosis, growth arrest, inhibition of cell cycle progression, cell differentiation, and DNA repair or senescence in response to genotoxic or cellular stress [4].

Different types of TP53 mutations were observed in 40% - 80% of EOC contributing either to an inactive or a truncated p53 protein. The majority of mutations affecting TP53 are usually located in exons 5–8, coding for the DNA binding domain of the protein. This domain plays a vital role in the activation of the transcription of p53 target genes [5].

The expression of p53 mutants is closely correlated with malignancy and prognosis of EOC, so it could be considered a prognostic indicator [6].

Aim of the work

To study the immunohistochemical (IHC) expression of FOX A1 and p53 in EOC and detect the relationship of their expression with the clinicopathological data of the studied cases, including (age, site of tumor, histological type, grade, stage of tumor, rupture of capsule and ascites).

Material and methods

This perspective and retrospective study was carried out on 52 cases with EOC, selected from archives of the pathology department, faculty of medicine, Aswan, and Sohag Universities in the period from January 2017 to December 2019. The specimens were collected as formalin-fixed, paraffin-embedded tissue blocks. The clinical information of the patients, including age, tumor size, histological type, grade according to World Health Organization (WHO), and stage according to FIGO staging were retrieved. The study was approved by the Ethics Board of Aswan University and informed written consent was taken from every participant in the study. The EOC cases previously-treated with neoadjuvant chemotherapy or radiotherapy and those with incomplete clinical data were excluded. Clinical and pathological data were collected from pathology reports including age, laterality of the tumor, ascites, capsular rupture, stage, histological type, degree of differentiation, and tumor grade were studied. Three serial sections from each tissue block were cut at 4 microns-thickness to be used as follows:

The first section was stained with routine Hematoxylin and Eosin (H&E) to confirm the histological diagnosis and tumor grade. The second section of slides was stained using the IHC technique with rabbit monoclonal antibody against FOX A1, A9793 at a dilution of 1:100. Negative control was run by omitting the primary antibody and positive control for FOX A1 was normal breast tissue. The third slide sections were stained with the rabbit monoclonal antibody against p53; A11232, 1ml concentration with a dilution of 1:100. Positive control for p53 was colorectal carcinoma. All cases were examined using a light microscope. The histopathological type according to the revised World Health Organization Classification of Tumors of the Female Reproductive Organs, were classified into serous, mucinous, endometrioid, and clear cell types [7].

Evaluation of FOX A1 IHC staining

For the evaluation of nuclear IHC staining results, immunoreactivity for FOX A1 in tumor cells was assessed using a scoring system based on staining intensity: negative = 0; 1% - 50% = 1; 51% - 75% = 2; and more than 75% = 3 [8].

Evaluation of p53 IHC staining

Immunoreactivity for p53 was evaluated according to the percentage of positive cells as follows: negative = 0; 1% - 50% = 1; 51% - 75% = 2; and more than 75% = 3 [9].

Statistical analysis of the data

Data were collected, tabulated, and statistically analyzed using Statistical Package for Social Science (SPSS) version 20.0. Qualitative data were described using numbers and percentages. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, and median. The significance of the obtained results was judged at the 5% level. The Chi-square test (X^2- test) was used to compare qualitative data such as different tumor grades and stages. Fisher's Exact or Monte Carlo correction: Cor-rection for chi-square when more than 20% of the cells have expected count >5. Student t-test was used in comparing one quantitative variable and one qualitative variable if they were normally distributed. F-test (ANOVA) for normally distributed quantitative variables, to compare between more than two groups. Mann Whitney test for abnormally distributed quantitative variables, to compare two studied groups. Kruskal Wallis test for abnormally distributed quantitative variables, to compare between more than two studied groups. Probability (p - value) difference considered as follow: Statistically significant (S) when ($p < 0.05$), highly significant (HS) when ($p < 0.01$) [10,11].

Results

This study involved 52 patients with OC and a median age of 53 years. Different histological types were included as 37 cases (7.2%) of serous, 12 cases (23.1%) mucinous, 1 case (1.9%) endometroid 2 cases (3.8%) clear cell OC. The study cases were classified into 22/52 cases (42.3%) Grade I, 16 cases (34.6%) Grade II, and 20 (48.5%) Grade III as shown in Table 1. Less than half of the cases 22 cases (42.3%) were at stage I, 9 cases (17.3%) at stage II, 11 (21.2%) at stage III, and 10 (19.7%) at stage IV. Bilateral OC was found in 31/52 cases (59.6%) and rupture of the capsule was detected in 30/52 cases (57.7%) while ascites were diagnosed in 29 cases (55.8%) (Table 1).

Assessment of IHC expression of both FOX A1 and p53 was done in malignant epithelial cells for IHC staining status,

pattern and intensity. FOXA1 showed a positive nuclear pattern of IHC expression in 38/52 cases (73.1%) and 14/52 (26.9%) were negative (Table 2). According to p53 IHC expression; all positive cases showed a nuclear pattern of expression. 35/52 cases (67.3%) showed positive IHC expression, while 17 cases (32.7%) showed negative expression (Table 3).

High significant correlation was found between FOX A1 expression, patient's age ($p = 0.010$), tumor stage ($p = 0.022$), histologic type ($p = 0.016$), tumor grade ($p < 0.001$), cases with ruptured capsule ($p = 0.001$) and ascites ($p < 0.001$) (Table 2).

No significant statistical association could be detected between FOXA1 expression and tumor site (unilateral or bilateral) in the studied cases (Table 2).

There was a high statistically significant association between p53 expression and histological type of the tumor ($p < 0.001$) (Table 3).

No significant correlation could be detected between age, tumor site (unilateral or bilateral), tumor grade, tumor stage, the status of the capsule (intact or reputed), ascites, and p53 expression (Table 3).

Table 1: The clinicopathological data of the studied cases (52 cases).

The clinicopathological data		No.	%
Age (years)	Min. – Max.	31:71	
	Mean ± SD.	52.27 ± 11.55	
	Median	53 y	
Tumour laterality	Unilateral	21	40.40%
	Bilateral	31	59.60%
Stage	22	I	42.30%
	9	II	17.30%
	11	III	21.20%
	10	IV	19.7
Histological type	37	Serous	71.20%
	12	Mucinous	23.10%
	1	Endometrioid	1.90%
	2	Clear cell	3.80%
Grade	14	Grade I	26.90%
	18	Grade II	34.60%
	20	Grade III	38.50%
Capsular rupture	30	Yes	57.70%
	22	No	42.30%
Ascites	29	Yes	55.80%
	23	No	44.20%

Discussion

Ovarian cancer (OC) is the second most common type of gynecological cancer worldwide, and it is a major cause of cancer-associated mortality in women [13]. There were an estimated 300,000 new ovarian cancer cases diagnosed worldwide in 2018 which was corresponding to 3.4% of all cancer cases among women. However, there is a substantial geographic variation in the burden of OC (rates are varying from 5.0/100,000 person/year in Africa to 9.5/100,000 person/year in Europe) [14].

The more practically accepted concept of classification

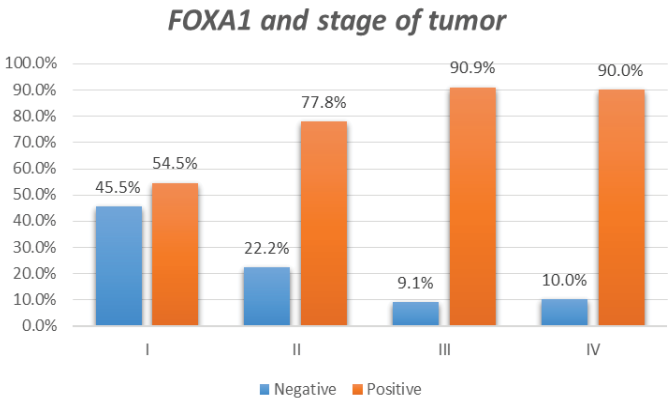

Figure 1: Relation between FOXA1 IHC positivity and stage of tumor.

Table 2: Relation between FOX A1 expression clinicopathological features.

		FOX A1			
		Positive ($n = 38$)	Negative ($n = 14$)	Test of Sig.	p
		No. %	No. %		
Age (years)	Mean ± SD.	54.74 ± 10.85	45.57 ± 11.04	t = -2.690	$p = 0.010$
Laterality	Unilateral	14 (66.67%)	7 (33.33%)	χ^2 0.736	$p = 0.391$
	Bilateral	24 (77.42%)	7 (22.58)		
Stage	I	12 (54.5%)	10(45.5%)		0.022
	II	7 (77%)	2(23%)		
	III	10 (90.9%)	1(9.1%)		
	IV	9 (90%)	1 (10.0%)		
Histologic type	Serous	27 (71.1%)	10(28.9%)		0.016
	Mucinous	11 (28.9%)	1(71.1%)		
	Endometrioid	-	1		
	Clear cell	-	2		
Grade	Grade I	3 (21.43%)	11 (78.57%)		< 0.001
	Grade II	16 (88.89%)	2(11.11%)		
	Grade III	19 (95%)	1 (5%)		
Capsule rupture	No	11 (50%)	11 (50%)	χ^2 10.322	0.001
	Yes	27 (90%)	3 (10%)		
Ascites	No	11(47.83%)	12 (52.17%)	χ^2 13.365	< 0.001
	Yes	27 (93.1%)	2 (6.9%)		

χ^2, p: χ^2 and p values for Chi-square test FEp: p - value for Fisher Exact for Chi-square test, MCp: p - value for Monte Carlo for Chi-square test t, p: t and p values for Student t - test

Table 3: Relation between p53 expression and the clinicopathological features of the studied cases.

		P53		Test of Sig	*p*
		Positive (*n* = 38)	Negative (*n* = 14)		
		No. %	No. %		
Age (years)	Mean ± SD.	53.69 ± 11.41	49.35 ± 11.61	*t* = -1.27	*p* = 0.207
Laterality	Unilateral	14 (66.67%)	7 (33.33%)	χ^2 0.007	*p* = 0.935
Stage	I	15	7		0.132
	II	6	3		
	III	9	2		
	IV	5	5		
Histologic type	Serous	35	2		< 0.001
	Mucinous	-	12		
	Endometrioid	-	1		
	Clear cell	-	2		
Grade	Grade I	9	5		0.634
	Grade II	11	7		
	Grade III	15	5		
Capsule rupture	No	16	6	χ^2 0.509	0.476
	yes	19	11		
Ascites	No	16	7	χ^2 0.096	0.757
	yes	19	10		

FEp: *p* - value for Fisher Exact for Chi-square test; MCp: *p* - value for Monte Carlo for Chi-square test *t*, *p* : *t* and *p* values for Student *t* – test.

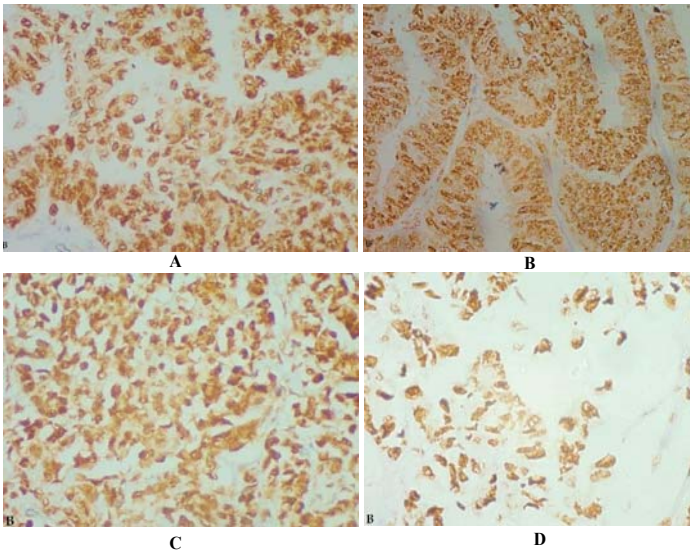

Figure 1a: Serous cystadenocarcinoma, (A) Grade I, (B) Grade II, and (C &D) Grade III, showed strong nuclear FOX A1 expression in tumor cells (IHC X 400).

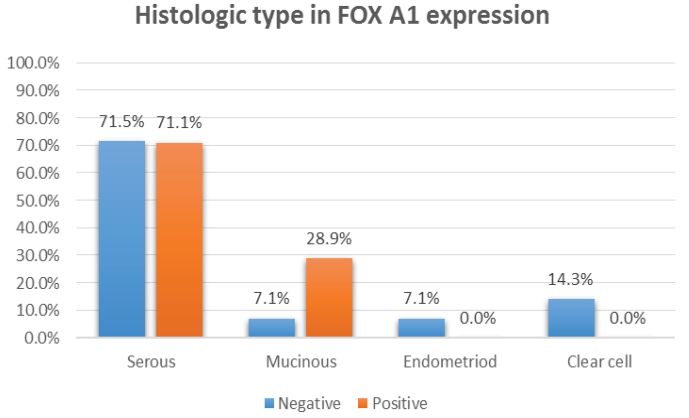

Figure 2: Relation between FOXA1 IHC positivity and histologic type.

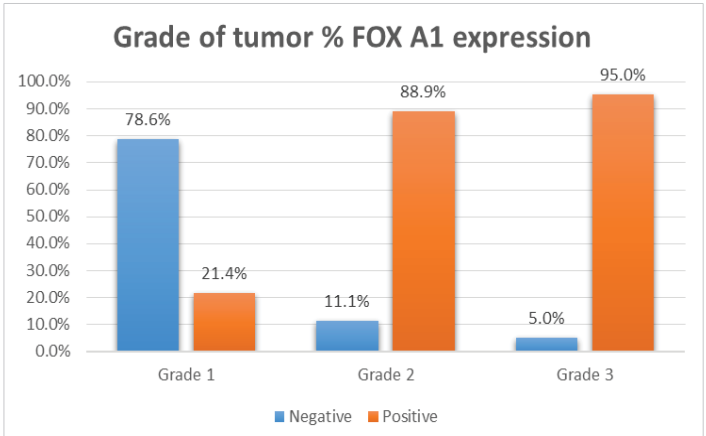

Figure 3: Relation between FOXA1 IHC positivity and grade of the tumor.

of OC is into 5 main histological types as follows: high-grade serous carcinoma (HGSC), clear-cell carcinoma, endometrioid carcinoma, mucinous carcinoma, and low-grade serous carcinoma (LGSC). This classification depends on differences in their biology, clinical presentation, and response to chemotherapy [15].

The current study aimed to evaluate the IHC expression of FOX A1 and p53 in tumor cells and their effect on the prognosis of EOC.

In this study, cases were patients of ages ranging from 31- 71 years. The mean age of the cases was 52.27 years, while the median age was 53 years. The age of the patients in this study was comparable to those reported by Wang, et al., who studied 110 cases of primary EOC and reported that the mean age of the patients was 54.5 years (range, 29–78 years) [16].

In the present work, bilateral tumors were the most

frequent (59.6%). This result was comparable to those reported by Wang, et al., as they reported that 46.4% of tumors were bilateral [16].

For histologic type, the current study denoted that more than (70%) of studied cases were serous carcinoma. Wang, et al., reported that 40% of tumors were HGSC. Also, Amanullah, et al., reported that 48.3% were serious tumors [16,17].

Regarding tumor grade, high-grade tumors were found to represent the highest percentage 73.0% of cases in the current research. This is in agreement with a study done by Ndukwe, et al., who reported that (66%) of tumors were high-grade neoplasms and (34%) of the case were low-grade neoplasms [18].

The state of the capsule and the presence of ascites are powerful prognostic factors and are routinely used to determine the stage of the tumor. In the current study, 57.7% of cases had ruptured capsules and 55.8% of cases had ascites, compared with 73% of cases that had ruptured capsules in the study of Amanullah, et al. [17].

In the current study, p53 expression using IHC staining was detected in (67.3%) of the studied cases. A previous study was done by Amanullah, et al., which reported p53 expression in (65.2%) of EOC samples. Furthermore, p53 positivity was detected in (58%) of EOC specimens according to a study carried out by Ndukwe, et al., on 50 specimens of EOC tissues. In contrast, a study carried out by Mohamed et al., showed a lower percentage (35.1%) of p53 expression in EOC [17-19].

In the current study, all p53-positive cases were serious malignancies. Malignant mucinous tumors, clear cell tumors, and endometrioid carcinoma cases were p53 negative. These results agree with Zhang, et al., who found strong p53 expression in (70.8%) of serous carcinomas and showed that the tumor histologic type was closely associated with the expression of p53 [20].

According to the relation between p53 expression and other clinicopathological variables; no significant association could be detected between p53 expression in tumor cells and other clinic-pathologic parameters including age, laterality, stage, state of the capsule, and presence or absence of ascites. This study showed no significant statistical relation between p53 expression and tumor grade in contrast to Ndukwe, et al., who had reported that p53 immunopositivity was significantly associated with high-grade tumors in general and high-grade serous carcinomas in particular [18].

Regarding Immunohistochemical expression of FOXA1 in EOC specimens; the present study demonstrated increased expression of FOXA1 in EOC tissues (73.1%). A study that was carried out by Wang, et al., reported that FOXA1 expression was seen in about 73.6% of EOC tissues [16].

According to the relation between FOXA1 expression and tumor stage; FOXA1 was positive in 90.48% of cases at stages III and IV. This result agreed with Zhang, et al., who detected FOXA1 in 84.7% of cases at stages III and IV [20].

In this study, a significant statistical relation could be detected between FOXA1 expression and tumor grade as 92.1% of tumors of grade II and grade III showed positive expression of FOXA1. This was concomitant with the study of Wang, et al., who observed that 41/62 cases of moderately differentiated and poorly differentiated EOC showed strong FOXA1 expression of tumor cells and that was statistically significant. These findings suggest that FOX A1 expression was associated with poor prognostic parameters in EOC [16].

In the current work; (71.1%) of positive FOXA1 expression cases were serous carcinomas of which (66.7%) and showed a significant relation between FOXA1 expression and histologic type of tumor. These results disagreed with Wang, et al., who reported that only 55% of serous carcinomas were stained positive with FOXA1. This discrepancy between results may be attributed to the difference in sample size [16].

According to the current work, there was a highly significant association between FOXA1 expression and tumors with ruptured capsules and ascites.

Conclusion

In conclusion, FOXA1 immunoexpression in EOC is considered a poor prognostic parameter as it is expressed in the majority of EOC, especially with advanced age, high grade, poor differentiation, advanced stages, tumors with ruptured capsule and ascites regardless of the side of the tumor (unilateral or bilateral). While p53 immunopositivity is significantly associated with the majority of cases of serous carcinoma, no significant association could be found between p53 immunoexpressing and other clinic-pathological parameters such as age, size of the tumor, tumor grade, stage, state of the capsule, and ascites. The results of the present study indicated that FOXA1 could serve an important function in EOC and may be a potential therapeutic target and prognostic marker.

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