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Original Article

A retrospective comparative study on epithelial ovarian carcinomas arising from and concomitant with endometriosis

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Abstract: Objectives: This study compares the clinical and pathological characteristics as well as prognosis among patients who are diagnosed of epithelial ovarian carcinoma arising from endometriosis (EOOC) and are just concomitantly with endometriosis (ECOC). Methods: A retrospective review, simultaneously from January 1995 to December 2014 at OB/GYN Hospital of Fudan University, involved patients diagnosed with epithelial ovarian cancer (EOC) and endometriosis, was performed. Firstly, the patients were divided into EOOC and ECOC according to whether there was a pathological continuity between EOC lesion and endometriosis or not. Then collect the clinical characteristics and pathological features of individual cases. And use logistic regression analysis to define the risk factors for EOOC. Finally, use the Kaplain-Meier method to compare the differences in overall survival and disease-free survival among groups. Results: The retrospective review identified 149 patients as EOC with endometriosis, and the result showed that there were 110 cases (73.8%) diagnosed with EOOC and 39 with ECOC. Compared with ECOC group, more patients with EOOC were at FIGO stage I (P<0.01) and took with clear cell carcinoma (P<0.01). The number of patients with ECOC that were diagnosed with FIGO stage II (P<0.01) or III (P<0.05) and high-grade serous adenocarcinoma (P<0.01) was larger. Logistic regression analysis showed that FIGO stage and tumor cell type were related risk factors for EOOC diagnosis. No significant difference in 5-year overall survival or disease-free survival was found among groups. Conclusions: Patients with EOOC or ECOC had a similar prognosis indicated by survival rates and carried with different FIGO stages and tumor histological types.

Keywords: Endometriosis, ovarian carcinoma, clear cell carcinoma, endometrioid carcinoma, prognosis

Introduction

In 2015, approximately 22,000 women in the United States were diagnosed with ovarian cancer and 14,000 of this died from the devastating disease, making it the most fatal gynecologic malignancy [1]. Endometriosis is a common gynecologic disease which is a benign condition but shares some characteristics of malignant disease such as tissue invasion, distant spread, unrestrained growth, angiogenesis and a decrease of apoptotic cells [2]. When operated for the malignancy, endometriosis was found concomitantly present with ovarian tumors in 4-29% of cases [3], which suggested that there was certain association between endometriosis and epithelial ovarian carcinoma (EOC). It was reported that ovarian tumors and adjacent endometriosis lesion shared common genetic alterations such as *PTEN (phosphatase and tensin homolog deleted on chromosome ten)* or *ARID1A* (*the AT-rich interactive domain 1A [SWI-like] gene*) mututions, which firmly suggested that there was a sequential or etiological correlation between endometriosis and EOC [4, 5]. The presence of metaplastic, hyperplastic, or atypical changes of endometriosis lesion had been observed, and the presence of these suggested that carcinoma might arise from endometriosis through a multi-step fasion [6].

Actually, the malignant transformation of endometriosis was first suggested and defined by Sampson as early as 1925: (1) clear evidence of endometriosis close to the tumor; (2) presence of tissue similar to characteristic epithelial glands surroundied by endometrial

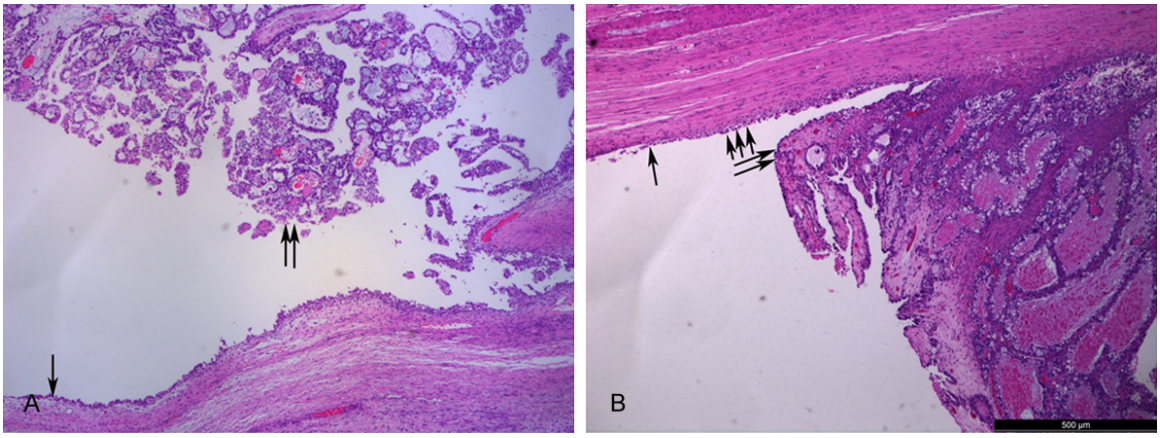

Figure 1. Representative pathological images. (A) was a case of ovarian clear cell carcinoma coexisting with endometriosis without proof of continuity. (B) was a case of ovarian clear cell carcinoma originated from endometriosis. The single arrow pointed to endometriosis lesion and the double arrow pointed to the clear cell carcinoma lesion. The triple arrow in (B) pointed to the transitional region between endometriosis and clear cell carcinoma, which is characteristic of enlarged hyperchromatic nucleus. Magnification in both figures ×200. The horizontal vertical scale bar represent 500 mm.

stroma; (3) exclusion of a metastatic tumor to the ovary [7]. Then Scott revised the criteria in 1953 and stressed that following standard should be conformed when defining endometriosis-originated ovarian carcinoma (EOOC): presence of benign endometriosis histological contiguous for the malignant tissue [8].

Up to present time, controversy still remains, for there is a possibility that EOOC might represent a distinct entity from other ovarian carcinomas. As a result, whether EOOC has distinct clinical or prognostic characteristics from ovarian carcinoma of other origins or not is a critical issue. However, we found that only one research had followed Sampson and Scott's criteria stringently in the English literature [9], although these criteria has been developed for more than sixty years. In most studies, the authors simply compare ovarian carcinoma patients with or without endometriosis [10]. Although some similar conclusions have been achieved by these two kinds of researches, for example, the study group is younger than the control group, we should be cautious when interpret the conclusions for the selection criteria is distinct in nature. Theoretically, concomitant present of EOC and endometriosis doesn't necessarily suggest a causal relation, instead they may only suggest identical risk factors shared by endometriosis and EOC.

In this study we compared the characteristics and prognosis of patients who diagnosed with EOOC and EOC only concomitant with endometriosis (ECOC). We tried to find out whether these two groups of patients are heterogeneous or not.

Methods

The study was approved by ethics committee of the hospital. Inform consents were obtained from all patients included.

We searched cases from the patient database of OB/GYN Hospital of Fudan University between January 1995 and December 2014. There are 2300 patients diagnosed of EOC histologically in this period. Of these, endometriosis had been diagnosed in 149 patients (6.48%), and this fullfill any one of the following situations: (1) presence of ovarian carcinoma and endometriosis in the same ovary (2) presence of ovarian carcinoma in one ovary and endometriosis in the contralateral ovary (3) presence of ovarian carcinoma and extra-ovarian endometriosis. These patients were denominated as endometriosis-associated ovarian carcinoma (EAOC) patients. On the contrary, patients affected by EOC without endometriosis were defined as non-EAOC patients. EAOC patients were then divided into two subgroups according to the Scott's criteria. EOOC was defined, as EAOC patients presenting exact proof about the continuity of carcinoma lesion from endometriosis in the pathological reports. And ECOC patients were the remaining patients whose continuity was not detected. Histopathology diagnosis followed the International Classification of Dis-

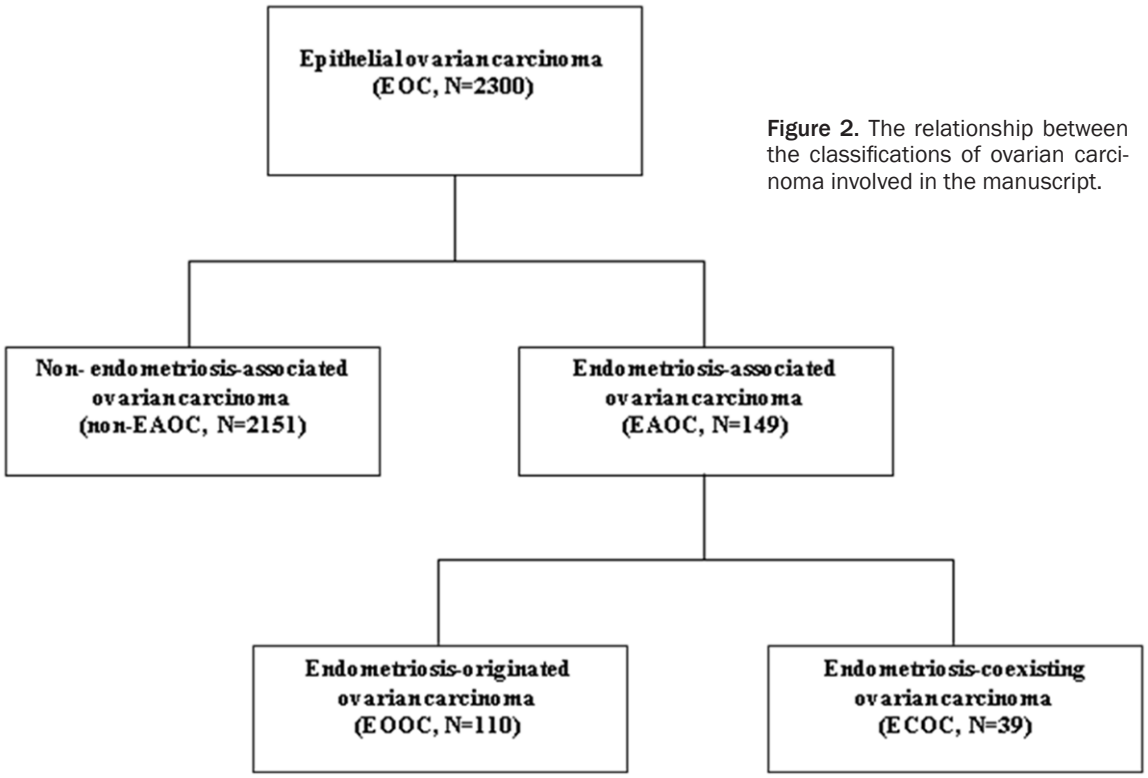

Figure 2. The relationship between the classifications of ovarian carcinoma involved in the manuscript.

ease for Oncology, 3rd edition (ICD-O-3) of World Health Organization (WHO). All the histological slides were reviewed by two related pathologists. The typical pathological characteristics of the two groups were shown in **Figure 1**. In **Figure 1B**, between the endometriosis and EOC lesion, the transitional region characteristic of enlarged hyperchromatic nucleus was presented. In **Figure 1A**, no continuity from endometriosis to EOC lesion was detected.

All patients underwent surgery, then received chemotherapy and finally were followed up according to our institutions. Patients' data was collected from the medical charts including age at diagnosis, ultrasonogram findings, surgery details, adjuvant chemotherapy, and the outcomes such as recurrence, death or survival. Optimal cytoreductive surgery was defined that the residual lesion of surgery was less than (or including) 1 cm. Patients were considered platinum-sensitive if the interval time, the period from the completion of the last platinum-based chemotherapy to recurrence, was more than 6 months.

The primary endpoint was the prognosis of patients in the two groups. We also compared the clinical and pathological characteristics between the two groups. Statistical analysis was accomplished by SPSS software (version 16.0, Chicago, IL, USA). When the continous samples fits normal distribution (when $P>0.05$ in Kolmogorov-Smirnov test), they were described as mean ± SD, and student's test would be used to compare the variables in clinical and pathological characteristics; and if not, they were described as median, and at that time, Mann-Whitney analysis would be used. The Pearson Chi-square test was used to analyze the differences of categorical variables between the two groups. Logistic regression analysis was used to calculate the risk factors that diagnosed EOOC in all the EAOC patients. Overall survival (OS) period was calculated from the date which contained from primary surgery to death or the last visit. Disease-free survival (DFS) was calculated from the date which contained from primary surgery to recurrence or last disease-free visit. Comparison between survival rates of both were completed with log-rank test in the Kaplan-Meier analysis. Finally, Cox regression model was used to account for the effect on potential confounding factors. A *p*-value smaller than 0.05 (two-sided) was considered statistically significant.

Table 1. Clinico-pathological features of patients in this study

Characteristics	The EOOC group (n=110)	The ECOC group (n=39)	*P* value
Age (y), mean ± SD	49.3±7.1	49.0±8.8	0.814
Gravid <2, % (range)	57.6 (n=99)	66.7 (n=27)	0.165
Parity <1, % (range)	23.2 (n=99)	22.2 (n=27)	0.881
Tumor size (cm), mean ± SD (range)	10.2±4.1 (n=98)	9.8±3.4 (n=30)	0.627
Serum CA-125 (U/ml), median (range)	38.4 (n=81)	95.7 (n=30)	0.030
CA-125 in normal range (<35 U/ml), % (range)	48.1 (n=81)	26.7 (n=30)	0.042
Pelvic lymph nodes positivity, % (range)	5.0 (n=101)	20.0 (n=30)	0.025
Cytoreductive surgery (%)	103 (93.6)	33 (84.6)	0.166
Laterality			
Left (%)	53 (48.2)	19 (48.7)	0.954
Right (%)	53 (48.2)	13 (33.3)	0.109
Both (%)	4 (3.6)	7 (17.9)	0.010
Histological types			
Clear cell carcinoma (%)	78 (70.9)	17 (43.6)	0.002
Endometroid carcinoma (%)	25 (22.7)	6 (15.4)	0.332
Endometroid and clear cell carcinoma (%)	1 (0.9)	0	1.000
Low-grade serous adenocarcinoma (%)	2 (1.8)	0	1.000
High-grade serous adenocarcinoma (%)	0	13 (33.3)	0.000
Mucinous adenocarcinoma (%)	1 (0.9)	3 (7.7)	0.094
Adenosquamous carcinoma (%)	3 (2.7)	0	0.567
With endometrial cancer (%)	5 (4.5)	0	0.327
FIGO Stage			
I (%)	94 (85.5)	17 (43.6)	0.000
II (%)	5 (4.5)	8 (20.5)	0.007
III (%)	10 (9.1)	13 (33.3)	0.010
IV (%)	1 (0.9)	1 (2.6)	0.456
Median cycles of chemotherapy	6	6	0.624
Chemosensitive	95 (86.4)	33 (84.6)	0.787
Status			
Relapse (%)	3 (2.7)	4 (10.3)	0.142
Dead (%)	8 (7.3)	6 (15.4)	0.241

The EOOC group: patients diagnosed with carcinoma arising from endometriosis. The ECOC group: patients diagnosed with carcinoma coexisting with endometriosis.

Results

During the study period, a total of 149 patients were diagnosed with EAOC. Among all, 110 (73.8%) patients were identified taking with EOOC, while the other 39 (26.2%) patients having no evidence on continuity from endometriosis were identified taking with ECOC (**Figure 2**).

Comparison of clinical and pathological features

The clinical and pathological parameters of the two groups were shown in **Table 1**. The average age of the overall patients was 49.5±7.5 years old (range, 21-78). Patients with ECOC had higher concentrations of the serum CA-125 (P=0.030).

More patients in the EOOC group were at FIGO stage I (85.5% *vs.* 43.6%) (P=0.000). On the contrary, more patients were at FIGO stage II (4.5% *vs.* 20.5%) (P=0.007) or III (9.1% *vs.* 33.1%) (P=0.010) in the ECOC group. And more patients were bilaterally involved (3.6% vs. 17.9%) (P=0.010) or they presented lymph node positivity (5.0% vs. 20.0%) (P=0.025) in the ECOC group.

The histological types also varied between two groups. The amount of clear cell carcinoma in the EOOC group was much more (70.9%

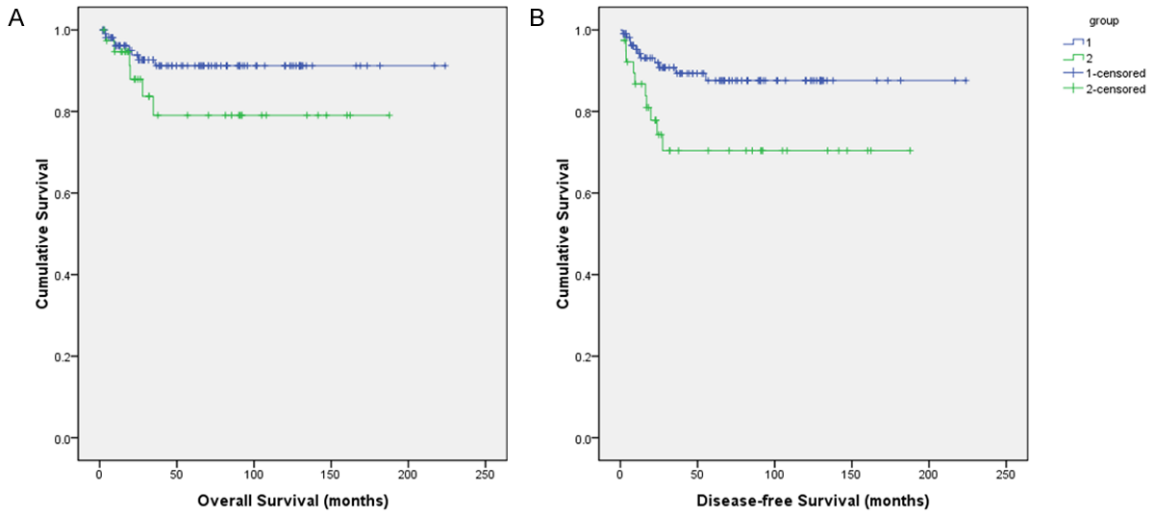

Figure 3. Survival curves for the Overall survival (OS) and Disease-free survival (DFS). A. OS curve of the two groups. B. DFS curve of the two groups. Group 1: patients diagnosed with ovarian carcinoma arising from endometriosis. Group 2: Patients were affected by ovarian carcinoma concomitant with endometriosis. There is significant difference between the DFS curves (P<0.05).

vs.43.6%) (P=0.002) than that in the ECOC group, while the number of patients with high-grade serous adenocarcinoma in the ECOC group was much more (0 *vs*. 33.3%) (P=0.000) than that in the EOOC group. However, the two groups had no significant difference in age, tumor size, gravidity, parity, chemotherapy regimen, cycles and chemosensitivity, as well as the proportion of patients receiving cytoreductive surgery. Although 5 patients were identified with endometrial cancer in the EOOC group and in the ECOC group there was no such one, no significant difference had been detected finally (P=0.327).

We used stepwise logistic regression to identify the risk factors of EOOC in all the EAOC patients. Variables such as age, tumor size, the level of serum CA-125, the unilaterality of the tumor, FIGO stage, as well as endometrioid/ clear cell histological type were all included into the equation. However, after iterations, only FIGO stage (exp(B)=0.49, 95% CI= 0.29-0.83, P=0.008) and endometrioid/ clear cell histological type (exp(B)=24.89, 95% CI=5.13-120.78, P=0.000) were found having the risk factors for identifying EOOC.

Comparison of survival outcome

After a median follow-up of 47 months (range, 2-224 months), 10 patients (6.7%) were out of observation during the follow-up. Fourteen cases of disease-specific deaths were observed. Estimated from Kaplan-Meier survival curves, respectively, the overall survival in 5 years (OS) was 91.2% for the EOOC group and 79.1% for the ECOC group, and no significance had been observed (P=0.111). Respectively the 5-year disease-free survival (DFS) was 87.6% for the EOOC group and 70.4% for the ECOC group; there is significant difference between them (P=0.013). **Figure 3** demonstrates survival curves of the two groups.

Because some features such as the FIGO stage, the CA-125 level, and the histological types are different between the two groups, we used Cox regression model to balance the influence of these factors. After that, we found that stage was useful prognostic factor for OS (exp(B)=4.68, 95% CI=2.40-9.13) (P=0.000) and for DFS (exp(B) =2.72, 95% CI=1.65-4.48) (P=0.000). There was no significant difference of disease-free survival between the two groups after ruling out the confounding factors (P=0.628).

Discussion

It was reported that compared with non-EAOC patients, EAOC patients have favorable characteristics such as younger age, earlier stage, and lower grade disease [2, 18]. But compared with non-EAOC patients, when strictly confine research object to EOOC patients, younger age

and more frequent unilateral ovarian involvement were also found during the research [9]. The authors explained these due to the typical symptoms of endometriosis, which may facilitate earlier diagnosis of EOC. On the contrary, ovarian malignancies irrelevant to endometriosis are mostly asymptomatic until advanced stages. In our cohort, we found there was no difference of age between the EOOC and the ECOC group. However, noteworthy difference of FIGO stage could be found. More patients in EOOC group were in FIGO stage I; while more patients in ECOC group were in FIGO stage II or III, they were bilaterally involved or they presented lymph node positivity. The histological types also varied, as more clear cell carcinoma in EOOC group and no high-grade carcinoma was identified. These results revealed that the ECOC patients were heterogeneous to ECOC patients in clinical characteristics.

Some research resumed that EAOC patients demonstrated a better prognosis than non-EAOC counterparts did [3]. However, after adjusting stage and age, no difference in survival between both was detected [2, 19, 20]. Comparison between EOOC patients and non-EAOC patients also indicated that there was no difference in survival between both [9]. In our study, after ruling out the confounding factors, no difference in survival was detected between EOOC and ECOC patients either. Together, these results suggests that endometriosis may not affect the progression after the onset of ovarian cancer [2].

Theoretically, if Scott's criteria was not followed strictly, the real frequency of malignant transformation might be overlooked because there might be patients having carcinoma coexisted with endometriosis independently. However, it was reported that Scott's criteria has rarely been fulfilled in practice [6]. The possible explanation is: (1) the tumor might have masked the deriving tissue of origin, which eliminates any histological evidence of endometriosis, (2) the demonstration of the histological contiguity between endometriosis and malignant tumors requires the extensive sectioning of the ovaries [3]. Even though it's precise, the rigorous criteria added by Scott may lead to the result that we underestimate the real frequency of malignant transformation of endometriosis. In reported studies, the frequency of identifying continuity of carcinoma lesion from endometriosis is much lower. In a series of 41 patients identified of clear cell carcinoma with endometriosis, only in 15 cases (36.6%), after in contiguity with endometriosis, the malignant lesions were found [11].

However, in our series, 73.8% of the EAOC patients were identified arising from endometriosis, which is much higher than the rates reported. It was noticed that if the pathologists took with a specific gynecological experience, the rates to detect malignancies arising from endometriosis is much higher, and *vice versa* [12]. This may be an important reason to explain the high frequency of identifying continuity, for our hospital is highly specialized in Gynecology field. It is also reported that at the stage of advanced malignancies, the frequency of detecting endometriosis is much lower, for the tumor might have masked the deriving tissue of origin [3]. Most patients (111/149, 74.5%) of our series are of FIGO stage I, which may explain the high frequency in another aspect. Logistic regression analysis also showed that early stage is a risk factor to identify EOOC patients.

Epidemiologically, endometriosis has been proved to increase the risk of EOC and the risk varying between different histological types. A pooled analysis of 13 case-control studies published in *Lancet* showed that self-reported endometriosis was associated with the significantly increased risk of ovarian clear-cell carcinoma (OR 3.05, 95% CI 2.43-3.84), endometrioid carcinoma (OR 2.04, 95% CI 1.67-2.48), and low-grade serous carcinoma (OR 2.11, 95% CI 1.39-3.20). No association was noted on mucinous carcinoma and high-grade serous ovarian carcinoma [13]. Pathologically, the synchronous presence of endometriod or clear cell carcinoma when endometriosis had been consistently reported to predominate over other subtypes [14]. A review of 15 published reports and concluded that 39.2% of ovarian clear cell carcinoma and 21.2% of ovarian endometrioid malignancies were with coexisting endometriosis, which were much higher compared with 3.0% of the mucinous type [15]. In our series, clear cell carcinoma and endometrioid carcinoma played a predominated role, while a low incidence of low-grade serous carcinoma is found in second position, which is in accordance with reported results [2]. Logistic regression analysis also showed that the endometri-

oid/clear cell histotype was a risk factor on identifying EOOC. Mucinous carcinoma and adenosquamous carcinoma that originate from endometriosis has also been sporadically found in the patients of our cohort. There were also such cases reported before [16, 17].

A dualistic model for carcinogenesis of EOC has been suggested. EOC can be divided into two types according to their origination, distinct molecular, clinical, and pathological characteristics. Type I is clinically indolent and usually show KRAS or BRAF mutations. However, type II is highly aggressive and usually presents TP53 mutation [16]. Besides, type I includes low-grade serous carcinoma, endometrioid carcinoma, clear-cell carcinoma, and mucinous carcinoma. It was suggested that they originate from ovarian benign cysts step by step through borderline tumor. High-grade serous carcinoma, carcinosarcoma, and undifferentiated carcinoma belong to Type II. Origination of type II is unclear and there is no proof of association with ovarian benign cyst such as endometriosis. In our study, we did not find type II carcinoma in EOOC patients either.

In closing, we acknowledge that our study has several limitations. It is retrospective in nature, which is of limited sample size, and differed in the follow-up period. However, as we know, it is the first study trying to distinguish EOOC and ECOC patients. We concluded that patients having ovarian carcinoma arising from endometriosis were heterogeneous to those who were concomitant with endometriosis in clinical characteristics such as FIGO stage and histological types. Nevertheless, there is no difference in prognosis between the two groups. Thus, we suggest that while carrying out research on EOOC patients, Scott's criteria should be followed. For more researches in the future, especially prospective trials should be used to confirm these results.

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Disclosure of conflict of interest

None.

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