RESEARCH ARTICLE

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Epithelial Ovarian Cancer with Endometriosis is not Associated with Menopausal Status: a Co-Association Study at Prapokklao Hospital

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Abstract

Objective: To determine any association between the menopausal status and epithelial ovarian cancer coexisting with endometriosis (EOC-E). In addition, the prevalence and possible risk factors were assessed. **Methods:** Medical records of 172 women with epithelial ovarian cancer between January 2011 and December 2016 at Prapokklao Hospital were reviewed and divided into two groups: EOC-E defined as the case group and without endometriosis (EOC-NE) as the control group. **Results:** The proportion of EOC-E was 18% (31/172). There were no significant differences between the two groups in baseline clinical characteristics and presenting symptoms except for history of smoking and abnormal uterine bleeding found more often in EOC-E cases. Most EOC-E were of clear cell histological type followed by endometrioid and serous types (35.5, 25.8 and 22.6 %; respectively). The clear cell type was 8 times more likely in the EOC-E than in the EOC-NE (OR 8.0, 95% CI 2.97-21.89, p-value <0.001) group. Nulliparity and smoking increased risk of EOC-E 2 and 7 times, respectively (OR 2.3, 95%CI 1.03-5.00, p-value 0.041 and OR 7.4, 95%CI 1.18-46.63, p-value 0.032). **Conclusions:** EOC-E are relatively common. Abnormal uterine bleeding is the only significant presenting symptom in the EOC-E as compared with the EOC-NE group. Endometriosis was a predictive factor for clear cell and endometrioid type I EOC. Menopausal status and age were not associated with a presentation of endometriosis with EOC.

Keywords: Epithelial ovarian cancer- endometriosis- prevalence- risk factors

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Introduction

Ovarian cancer (OC) is the sixth most common occurring cancer in women in Thailand (Imsamran et al., 2015). It consists of two subtypes: common epithelial ovarian cancer (EOC) and non- epithelial ovarian cancer (germ cell, sex cord and stromal type), found at ninety and ten percent in OC cases respectively (Berek et al., 2012). Advance stage of OC came from late diagnosis, incomplete debulking surgery, poor general medical conditions and lack of effective screening methods, those will lead to other complications and poor prognostic outcome (Wentzensen et al., 2016).

Risk factors of EOC can be classified as genetics and non-genetic factors. Genetic factors usually came from gene mutations, especially the hereditary factors germline and somatic mutation in BRCA1 and BRCA 2 of high grade serous carcinoma EOC (Kurman and Shih, 2010) which transmitted to daughter by incomplete penetrance. Smoking, obesity, contraception, high fat diet, infertility, endometriosis and co-morbid diseases were suspected to be its non-genetic causes (Munksgaard et al., 2011).

Nowadays, ovarian tumors may be separated into two groups as type I and type II. Type I tumors are slow growing tumor and confined to the ovary at diagnosis which develop from well- established precursor lesions. In contrary, type II tumors are rapidly growing tumor and highly aggressive which inappropriate precursor of lesions (Kurman and Shih, 2010)

Endometriosis is an extra-uterine implantation of gland and stromal of endometrium (Berek et al., 2012). It is a common problem with multiple symptoms and disease variation (Krawczyk et al., 2016). The origin of epithelial ovarian cancer with endometriosis (EOC-E) has a different malignant potential which been classified in the category of low grade ovarian cancer (type I) (Kurman and Shih, 2008). Molecular alteration seen in endometriosis may be a precursor lesion for EOC, especially those of clear cell and endometrioid histology (Bounous et al., 2016; Del Carmen, 2015).

The purpose of this study was to demonstrate prevalence and risk factors in EOC-E and epithelial

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ovarian cancer without endometriosis cases (EOC-NE). Clinical association between OC and endometriosis were investigated in hope of finding any relevant relationship between the two. Demographic data including age, body mass index (BMI), parity, race, menopausal status, smoking, contraceptive methods, stage, presenting symptoms and histological finding were also investigated.

Materials and Methods

Institutional approval and informed consent

This study was a descriptive study in Prapokklao Hospital, Chantaburi, Thailand. Ethical approval was approved by the Prapokklao Hospital Institutional Review Board No CTIREC 056/59. Inform consent did not require base on agreement of the Prapokklao Hospital Institutional Review Board.

Patient populations

This study was recruitment of all the medical record of EOC cases between January 2011 and December 2016. The inclusion criteria was all newly diagnosed EOC patients confirmed by gynecologic oncologist. Exclusion criteria were recurrent EOC and cases of non-histological proven endometriosis. All of EOC-E cases were re-confirmed by pathologist.

Data collection

Medical records of EOC patients were reviewed. The subjects were divided into two groups, EOC-E and EOC-NE. Data collection were baseline demographics data such as age at the time of diagnosis, body weight, height, BMI, parity, race, marital status, contraceptive methods, stage that determined according to International Federation of Gynecology and Obstetrics (FIGO) (Zeppernick et al., 2014), ultrasound finding, risk of malignancy index (RMI) (Jacob et al., 1990), clinical presentations and histological assignment based on the world health organization (WHO) Classification 2014 of OC (Meinhold-Heerlein et al., 2016). Data between two groups were compared.

Computerized commercial statistical program in this study was Stata12 (Stata Corp LLC, Texas, USA). Continuous data was represented in the form of percentage, mean and standard deviation. Categorical data was calculated with Fisher's exact or Chi-square test. The p-value less than 0.05 was classified as statistical significance.

Results

Patient's characteristics

During the five years of study period, 172 cases of EOC that had been diagnosed and treated by surgery and chemotherapy were recruited. According to the pathological criteria 31 (18%) patients were identified as EOC-E and 141 (82%) patients as EOC-NE (Table 1). The prevalence of endometriosis in EOC cases was 18% (31/172).

Mean age at diagnosis was 51.4 and 52.4 years old for EOC-E and EOC-NE, respectively. The demographic data are presented in Table 1.

Two-third of ultrasound finding in all EOC cases was of mixed solid cystic pattern. Mean serum level of CA-125 in EOC-E and EOC-NE were not significant difference at 1,152.3 and 1,836.7 IU/ml respectively. Seventy seven and eighty two percent of EOC-E and EOC-NE cases had

Table 1. Demographic Characteristic of Women between EOC-E and EOC-NE

Characteristic	EOC-E (n=31)*	EOC-NE (n=141)*	p-value
Age**	51.4 (±10.1)	52.4 (±11.9)	0.684
<50	13 (41.9)	51 (36.2)	0.546
≥50	18 (58.1)	90 (63.8)	
Ethics			1
Thai	30 (96.8)	135 (95.7)	
Non-Thai	1 (3.2)	6 (4.3)	
Status			0.08
single	13 (41.9)	36 (25.5)	
marriage	18 (58.1)	105 (74.5)	
Parity			0.061
nulliparity	16 (51.6)	45 (31.9)	
Primi-multiparity	15 (48.4)	96 (68.1)	
BMI			0.679
Obesity+	11 (35.5)	45 (31.9)	
Non-obesity++	20 (64.5)	96 (68.1)	
Smoking	3 (9.7)	2 (1.4)	0.041
Contraception			0.418
Hormonal	28 (90.3)	117 (83.0)	
Non-hormonal	3 (9.7)	24 (17.0)	
Underlying disease†			0.141
Yes	14 (45.2)	43 (30.5)	
No	17 (54.8)	98 (69.5)	
Family history of cancer	6 (19.4)	15 (10.6)	0.222
Menopausal status			0.527
Pre	11 (35.5)	42 (29.8)	
Post	20 (64.5)	99 (70.2)	
Ultrasound finding**			
Mixed solid cystic	19 (61.3)	98 (69.5)	0.399
CA125**	1152.3 (±2443.5)	1838.7 (±5827.8)	0.52
<35	14 (12.0)		0.009
≥35	17 (88.0)		
RMI >200	24 (77.4)	115 (81.6)	0.617
FIGO stage			0.596
I	12 (38.7)	37 (26.2)	
II	2 (6.5)	10 (7.1)	
III	6 (19.4)	37 (26.2)	
IV	11 (35.5)	57 (40.4)	
Early- stage disease			0.221
FIGO stage I-II	14 (45.2)	47 (33.3)	
Advance-stage disease			
FIGO stage III-IV	17 (54.8)	94 (66.7)	

*, n (%); **, mean + standard deviation (SD); EOC-E, epithelial ovarian cancer coexisting with endometriosis; EOC-NE, epithelial ovarian cancer coexisting without endometriosis; +obesity, BMI (body mass index) ≥23; ++non–obesity, BMI<22.9; † underlying disease, diabetes mellitus, hypertension, thyroid disease, autoimmune disease and hematological disease; RMI, risk of malignancy index

Table 2. Presenting Symptoms in EOC-E and EOC-NE

Presenting symptom	EOC-E (n=31)*	EOC-NE (n=141)*	p-value
Pelvic mass	18 (58.1)	66 (46.8)	0.32
Pelvic pain	3 (9.7)	10 (7.1)	0.7
GI*	4 (12.9)	38 (26.9)	0.11
GU**	0	0	0
AUB†	4 (12.9)	5 (3.6)	0.049
Ascites	1 (3.3)	7 (4.9)	1
Weight loss	0	1 (0.7)	1
Pleural effusion	0	2 (1.4)	1
Bowel obstruction	0	0	0
Mixed symptoms	0	13	0.12

, n (%); EOC-E, epithelial ovarian cancer coexisting with endometriosis; EOC-NE, epithelial ovarian cancer coexisting without endometriosis; GI, gastrointestinal symptom; ** GU, genitourinary symptom; † AUB, abnormal uterine bleeding

RMI more than 200 respectively (Table1) that was not significant difference.

FIGO staging classifications (Zeppernick et al., 2014) of EOC-E group were 12 (38.7%), 2 (6.5%), 6 (19.4%), 11 (35.5%) in the stage I, II, III, IV; respectively. FIGO staging classifications was showed in Table1. EOC-E group mostly in the advance stage of disease (FIGO stage III-IV) that was not significant difference.

Clinical characteristics

The presenting symptoms of two study groups are shown in Table 2. Nearly half of the EOC cases were presented with abdominal mass. The percentage of abnormal uterine bleeding (AUB) in EOC-E group was significantly higher than EOC-NE group (12.9 and 3.6%, respectively, p–value 0.049). The other presenting symptoms such as gastrointestinal, genitourinary, ascites, weight loss, pleural effusion and bowel obstruction showed no significant difference between two groups (Table 2).

The comparison between histology of EOC-E and EOC-NE is present in Table 3. EOC-E showed the highest

Table 3. The Comparison between Histology of EOC-E and EOC-NE

Histology	EOC-E (n=31)*	EOC-NE (n=141)*	p-value
Serous	7 (22.6)	44(31.2)	0.39
Endometrioid	8 (25.8)	24 (17.0)	0.3
Mucinous	2 (6.5)	28 (19.9)	0.11
Clear cell	11 (35.5)	9 (7.1)	<0.001**
Brenner	0	0	0
Mixed EOC	1 (3.2)	4 (2.84)	1
Undifferentiated	2 (6.5)	31 (22.0)	0.040**

*, n (%); EOC-E, epithelial ovarian cancer coexisting with endometriosis; EOC-NE, epithelial ovarian cancer coexisting without endometriosis; **, p- value<0.05.

percent of cases in clear cell type [11 (35.5%)] while EOC-NE group showed 44 cases (31.2%) in serous type. Histological subtype of EOC-E revealed endometroid and serous adenocarcinoma at 25.8 and 22.6 %. The histological subtypes of EOC-NE were presented as serous, undifferentiated, mucinous, endometrioid, clear cell and mixed EOC at 31.2, 22.0, 19.9, 17.0, 7.1 and 2.8%, respectively.

Clear cell histological type in EOC-E was significantly found at 8 times higher incidence compared to the same type found in EOC-NE group at p –value <0.001. EOC-NE group had more incidence of undifferentiated cell type than EOC-E group at 22.0 and 6.5 % respectively (Table 3).

Nulliparity is present in Table 4. It was twice more likely to be associated with EOC-E when compared to multiparity (OR 2.3, 95%CI 1.03-5.00, p-value 0.041). Smoking women had seven times higher risk of EOC-E (OR 7.4, 95%CI 1.18-46.63, p-value 0.032). Clear cell type of EOC has eight times higher association with EOC-E than EOC-NE (OR 8.0, 95% CI 2.97-21.89, p-value <0.001).

Discussion

The number of EOC cases found at Prapokklao Hospital

Table 4. Univariate and Multivariate Logistic Regression to Determine Factor Associated with Endometriosis

Characteristic	Univariate analysis			Multivariate analysis		
	Odd ratio	95%CI	p-value	Odd ratio	95%CI	p-value
Parity						
Nulliparity	2.3	1.03-5.00	0.041*	2.1	0.85-4.98	0.105
Smoking	7.4	1.18-46.63	0.032*	11.3	1.61-79.89	0.015*
Histology						
Clear cell	8	2.97-21.89	<0.001*	9.32	3.26-26.67	<0.001*
Endometrioid	1.8	0.74-4.74	0.18			
Serous	0.6	0.26-1.65	0.382			
Infertile	2.5	0.69-8.76	0.164			
Suboptimal surgery	0.4	0.20-1.00	0.052*	0.5	0.19-1.16	0.106
RMI>200	0.7	0.30-1.99	0.597			
OCP	1	0.28-3.95	0.937			

EOC-E, epithelial ovarian cancer coexisting with endometriosis; *p-value<0.05*

increases annually. Multiple risk factors are correlated with EOC. Etiology of ovarian cancer is associated with low parity, early menarche, late menopause and infertility (Berek et al., 2012). The incidence of endometriosis in general population was approximately 10% (Dinkelspiel et al, 2016) especially in women at reproductive age (Krawczyk et al, 2016). However, endometriosis had increased risk of EOC in many study (Verit et al., 2013).

Endometrioid and clear cell OC share a similar, unique pattern of associations with increased risks among women with endometriosis and decreased risks associated with tubal ligation (Berek et al., 2012).

The prevalence of epithelial ovarian cancer coexisting with endometriosis in this study was 18%. Our finding was higher than 3.4% reported eleven years ago from northern Thailand (Surprasert et al., 2006). The incidence of EOC-E reported in Asia and Europe was 14.5% and 4.2-11.3% (Surprasert et al., 2006; Jimbo et al., 1997; Scully et al., 1966; Sainz et al., 1996)

Half of patients in EOC-E group with nulliparity reported twice more risk for EOC-E. The finding agrees with previous (Berek et al., 2012). The significant differences between EOC-E and EOC-NE in this investigation showed in history of smoking that the mechanical correlation still unknown. Wentzensen reported similar association between smoking and EOC especially for mucinous epithelial ovarian cancer (Wentzensen et al., 2016).

In this study, result has a higher percentage of EOC from endometriosis cases than Thai data from ten years ago (Surprasert et al., 2006). However, our number is compatible to recent reports worldwide. Mean age of EOC-E in our study was 51.4 years old and was no significant difference from that of women in EOC-NE group. In our population, 64.5% EOC-E patients was in post-menopausal compared to 35.5% premenopausal group. In EOC-NE 70.2% patients was in postmenopausal compared to 29.8% premenopausal patients of the same condition. Our data showed that epithelial ovarian cancer with endometriosis was not associated with hormonal status both in EOC-E and EOC-NE groups.

The role of the nuclear and cytokine receptor families in ovarian cancer has been well established. Estrogen has been implicated in the progression of ovarian cancer, where estrogen transduces pro-metastatic pathways via the nuclear estrogen receptor (ER). Recent epidemiological studies have demonstrated an elevation of ovarian cancer incidence with the postmenopausal use of estrogen (Rodriguez et al., 2001; Hein et al., 2013). Our study has higher percentage of EOC cases in postmenopausal subjects. Their age of menarche, contraceptive history, lactation history, and postmenopausal management should be investigated to see if they have any correlation to OC prevalence.

Endometriosis is a disease that hormonal dependent and mostly found in premenopausal status. In this study it was found consistently in both study groups that age was not factor contributing to EOC-E and EOC-NE. Premenopausal and postmenopausal status were not a factor to define endometriosis because of in both group shown no statistical different. This finding may be explained by the work of Haidarali in year 2016 that EOC-E associated with reduction of estrogen receptor (ER) expression (Haidarali et al., 2016). While Thomsen and co-worker reported in year 2017 that hyperestrogenism (endogenous or exogenous) and/or cysts with solid compartments may have an elevated risk of epithelial ovarian cancer (Thomsen et al., 2017). In our opinion, based on our data endometriosis can be a coincidence with EOC but not a causative of malignant transformation. This finding supported the previous data that malignant transformation from endometriosis was rare occurrence (Taniguch, 2017).

Thomas reported association between endometriosis and an increased risk of gynecologic malignancy (Thomas et al., 2012). Endometrioid and clear cell subtype of ovarian cancer were associated with endometriosis in work done by Heidemann and coworker (Heidemann et al., 2014). EOC-E in western countries was commonly presented with clear cell EOC and endometrioid EOC (8-49 and 9-39%) (Kurman et al., 1972; Russell et al., 1979). This is similar to that reported in Tokyo, Japan (Jimbo et al., 1997) and Chiangmai, Thailand (Surprasert et al., 2006). Our data supported the mentioned finding; common prevalence of histological subtype in EOC-E was clear cell type followed by endometrioid type and then serous type that demonstrated in (11/31) 35.4%, (8/31) 25.8% and (7/31) 22.5% respectively.

The histological pathology of EOC was classified by WHO Classification of Ovarian Cancer (Meinhold-Heerlein et al., 2016). One third of EOC cases were serous type (51/172) that was similar to that of the general population in the other countries. Based on the data from histological subtype, clear cell type was the most commonly found in EOC-E than in EOC-NE whereas undifferentiated cell type was more common in EOC-NE with statistical significant.

Limitations of this study may be from the small number of populations and prognostic outcome could not be identified because of retrospective study. From the new WHO Classification of Ovarian Cancer published 2014 (Meinhold-Heerlein et al., 2016), the histological confirm in subtype of serous adenocarcinoma (Kurman and Shih, 2010) can't be evaluation due to lack of pathological review with immunohistochemistry.

In conclusion, prevalence of EOC-E in our institute was 18 %. Clear cell adenocarcinoma was mostly found in EOC-E. Baseline clinical characteristic was difficult to use as the screening methods for detection of abnormal and high risk patients on EOC. Abnormal uterine bleeding was statistical significant of EOC-E. Endometriosis was mostly found in one quarter of serous carcinoma. Endometriosis coexisting with epithelial ovarian cancer in this study was not correlated with younger age or menopausal status. However, continuous treatment of endometriosis should be in highly precaution especially in postmenopausal women.

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Statement conflict of Interest

The authors declare no conflict of interest.

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