RESEARCH ARTICLE

Does Endometriosis Hinder Successful Ovarian Debulking Surgery?

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Abstract

Background: Endometriosis has a significant effect on many aspects of women's lives, also increasing the risk of ovarian cancer. Although endometriosis is considered as a benign condition, it sometimes behaves like cancer. **Methods:** All medical records of epithelial ovarian cancer patients during January 2011 to December 2016 were reviewed. Recurrent cases were excluded. Data collected included age at diagnosis, parity, marital status, familial history of cancer, menopausal status, weight, height, smoking histroy, contraception, CA 125 level, result of surgery and pathological report. **Results:** One hundred and seventy-two medical records of patients with epithelial ovarian cancer (EOC) were included. Average age at diagnosis was 52.3 years. Epithelial ovarian cancer coexisting with endometriosis (EAOC) was found in nearly one-fifth of cases. Nullipara and smoking were associated with 2.3 and 8.3 fold higher risk of EAOC development (aOR 2.349, 95%CI 1.012-5.451; aOR 8.26, 95%CI 1.234-55.278; respectively). Age, familial history of cancer and coexistence with endometriosis were factors related to surgical outcome. More of EAOC group had optimal surgery compared to the non-EAOC group (61.3% and 41.8%) with statistical significance. **Conclusion:** Younger age, familial history of cancer and coexistence of endometriosis were factors related to optimal surgery. Success of optimal surgery is greater in EAOC than in non-EAOC patients. Coexistence of endometriosis does not hinder successful ovarian cancer debulking surgery.

Keywords: Epithelial ovarian cancer- endometriosis- optimal surgery

Introduction

Endometriosis is a predominantly estrogen-dependent disease composed of extrauterine deposit of endometrial gland and stroma. Ninety percent of reproductive women with chronic pelvic pain or infertility showed some degree of endometriosis (Somigliana et al., 2006; Suh et al., 2013). Surgical diagnosis of endometriosis reported to be 1.3 to 1.6 per 1,000 women of reproductive age (15 to 49 years of age) (Missmer et al., 2003). Although endometriosis was considered as a benign condition, it sometimes behaved like an ovarian cancer with angiogenesis, unrestrained growth, tissue invasion and a decrease in the number of cells undergoing apoptosis (Kim et al., 2014). Despite the invasive and destructive nature of endometriosis, most cases were always benign and finally regress; though, atypical endometriosis was a precursor lesion that could lead to some types of ovarian cancer (Wei et al., 2011). American Society for Reproductive Medicine (ASRM) classified the extent of endometriosis to four stages: minimal, mild, moderate and severe. Unfortunately, these stages did not clearly represent the severity of the disease. Currently, the etiology of endometriosis is still unknown (Bulun, 2009).

The incidence of ovarian cancer is relatively low when compared to cancer of breast, colon, cervix, lung, corpus uteri and stomach (Ferlay et al.,2013). The incidence is 5.0-9.4 per 100,000 women-year and cumulative risk is 0.5-1.0% globally (Jemal et al., 2011). In Thailand, it is currently the sixth most common cancer after cervix, breast, liver, lung and colon (Ferlay et al., 2013). Endometriosis was associated with 1.2-1.8 times increased risk of ovarian cancer (Kim et al.,2014). A successful operation performed in endometriosis patient was difficult due to so much endometriosis deeply implant in the abdominal cavity. It can decrease the ability of surgeons to reach as much as cancerous tissue as should be removed. Aim of this study was to evaluate whether the existent of endometriosis had any association with suboptimal surgery of ovarian cancer.

Materials and Methods

This research was approved by Prapokklao Hospital Institutional Review Board. All medical records of the patients with epithelial ovarian cancer who attend our

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gynecologic oncology unit between January 2011and December 2016 were reviewed. Exclusion criteria were the patients with recurrent epithelial ovarian cancer. Data collected include age at diagnosis, parity, marital status, familial history of cancer, menopausal status, weight, height, smoking, contraception, CA 125, result of surgery and pathological report.

Diagnosis of endometriosis is defined as existence of endometriotic tissue from pathological report. The risk of malignancy index (RMI) is a scoring system of various clinical feature combination. It is calculated based on the serum CA 125 value, menopausal status (M), and evaluation of ultrasound (U) as proposed by Jacob et al (Jacob et al., 1990). It was used for preoperative assessment of ovarian cancer possibility.

Less aggressive ovarian cancer subtypes were serous, mucinous and Brenner tumor whereas more aggressive subtype included clear cell, mixed epithelium and undifferentiated cell type. Optimal surgery composed of total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritoneal washing, pelvic and paraaortic lymphadenectomy with no tumors larger than one centimeter left behind. Early stage cancer was defined as FIGO stage I and II while advanced stage was FIGO stage III and IV (Berek et al., 2012)

Data were analyzed using the Statistical Package for the Social Sciences Version 17 (IBM, Armonk, NY, USA). The characteristic data were compared between optimal vs suboptimal surgery and epithelial ovarian cancer coexisting with endometriosis (EAOC) vs non EAOC using an unpaired t-test, a chi-square test and multivariate logistic regression. A p-value of less than 0.05 was considered statistically significant.

We investigated the impact of EAOC on the risk and prognosis for ovarian cancer treatment in comparison with non-EAOC

Results

There are 172 epithelial ovarian cancer (EOC) patients included in the study. EAOC found nearly one-fifth of all EOC (18.0%). Mean age of the population at diagnosis is 52.3±0.9 years old. Most patients (95.9%) are Thai citizen. Two-third of cases (64.5%) are multiparity. Nearly one third of the population (32%) are obese. Familial history of cancer present at 12.2%. Nearly one- third are found in the more aggressive pathological subgroup (Table 1).

Odd ratio of factors related to EAOC was showed in Table 2. Nullipara and smoking showed 2.3 and 8.3 times higher risk for developing EAOC (aOR 2.349, 95%CI 1.012-5.451, p-value 0.047; aOR 8.26, 95%CI 1.234-55.278, p-value 0.029; respectively). No correlation of age, obesity, oral contraceptive use and RMI score to EAOC were shown.

Percentage of optimal surgical removal of cancer was higher in EAOC than that of non-EAOC group (61.3 and 41.8%, respectively) with statistical difference. Percentage of early stage of ovarian cancer found 45.2% and 33.3% in

Table 1. Demographic Characteristics of the Study Population Relate to Result of Surgery (n=172)

Characteristics		Result of surgery		p-value
	All N=172	Optimal Sx78 (45.3%)	Sub-optimal Sx 94 (54.7%)	
Age (Mean ±SD)	52.3±0.9	51.0±10.0	53.4±12.7	0.048*
Diagnosis of endometriosis	31	19 (61.3)	12 (38.7)	0.049*
Familial history of cancer	21	14 (66.7)	7 (33.3)	0.036*
Postmenopause	123	52 (43.7)	67 (56.3)	0.514
CA 125(Mean ±SD)	1713.35±410.1	1362.8±420.8	2004±664.9	0.196
RMI >200	139 (80.8)	63 (80.8)	76 (80.9)	0.989
Pathologic subgroup				0.226
Less aggressive cell type	113 (65.7)	55 (48.7)	58 (51.3)	
More aggressive cell type	59 (34.3)	23 (39.0)	36 (61.0)	

*statistical significant; EAOC, epithelial ovarian cancer coexisting with endometriosis; non-EAOC, epithelial ovarian cancer not coexisting with endometriosis; Less aggressive subtype, serous, mucinous and Brenner; more aggressive subtype, clear cell, mixed epithelium and undifferentiated; Sx, surgery; RMI, Risk of malignancy index.

Table 2. Odd Ratio of Factor Related to Epithelial Ovarian Cancer Coexisting with Endometriosis

Factors	Crude odd ratio	95%CI	p-value	Adjusted odd ratio	95% CI	p-value
Age	0.992	0.960-1.026	0.646	0.999	0.963-1.036	0.96
Obesity	1.212	0.535-2.746	0.644	1.174	0.500-2.757	0.713
Nullipara	2.276	1.034-5.006	0.041*	2.349	1.012-5.451	0.047*
OCP use	1.055	0.077-5.082	0.662	0.911	0.225-3.696	0.897
RMI >200	0.775	0.302-1.991	0.597	1.475	0.550-3.952	0.44
Smoker	7.446	1.189-46.638	0.032*	8.26	1.234-55.278	0.029*

*statistical significant; Obesity defined as body mass index (BMI, body weight (kgs)/ height (meter)^2) more than 24.9; OCP, oral contraceptive pill; RMI score (malignancy risk index) is calculated based on the serum CA 125 value, menopausal status (M), and evaluation of ultrasound (U). The formula is: RMI, U x M x CA125.

Table 3. Comparison of Result of Surgery between Epithelial Ovarian Cancer Coexisting with Endometriosis and Epithelial Ovarian Cancer NOT Coexisting with Endometriosis

			Epithelial ovarian cancer			p-value
			All N=172	Non-EAOC N=141	EAOC N=31	
Result of surgery						0.049*
	Optimal		78 (45.3)	59 (41.8)	19 (61.3)	
	Sub-optimal		94 (54.7)	82 (58.2)	12 (38.7)	
Stage						0.003*
	Early stage		61 (35.5)	47 (33.3)	14 (45.2)	0.197
		Optimal	44 (72.1)	32 (68.1))	12 (85.7)	
		Suboptimal	17 (27.9)	15 (31.9)	2 (14.3)	
	Advance stage		111 (64.5)	94 (66.7)	17 (54.8)	0.305
		Optimal	34 (30.6)	27 (28.7)	7 (41.2)	
		Suboptimal	77 (69.4)	67 (71.3)	10 (58.8)	

*statistical significant; EAOC, epithelial ovarian cancer coexisting with endometriosis; non-EAOC, epithelial ovarian cancer NOT coexisting with endometriosis; Early stage defined as FIGO stage I and II; Advanced stage defined as FIGO stage III and IV.

EAOC and non-EAOC group, respectively with statistical significant. Advanced stage of ovarian cancer found more in non-EAOC group than in EAOC with statistical significant. Subgroup analysis of suboptimal surgery in advanced stage of both EAOC and non-EAOC showed no statistical different between the two groups (Table 3).

Discussion

Ovarian cancer is found worldwide. Our investigation revealed average age of participants at 52.3 years old. The age group is compatible with finding from other research. Out of this total, 31 out of 172 (18.0%) revealed coexisting with endometriosis. Szubert et al., (2016) from Poland reported that there was no EAOC in 394 ovarian cancer cases. The study of Ye et al., (2014) from China found an EAOC in 37.7% (79/210). On the other hand, the study of Kim et al., (2015) from Korea found that the prevalence of EAOC was nearly half of ovarian cancer cases (47/109).

All patients in this study underwent surgical staging operation by gynecologic oncology surgeon. In our experience, we felt that the optimal debulking surgery (remain cancerous lesion of less than one centimeter) was more difficult in patients with endometriosis. It turned out that in patients with early stage, percentage of optimal or suboptimal surgeries were statistical non-significant. Ovarian cancer patients who had coexisting with endometriosis were younger than the cancer only group (non-EAOC) with statistical significant (Table 1), even though the average age different was only 2.4 years.

The study of Ye et al., (2014) found that patients in EAOC group (79/210) had average age less than patients in non-EAOC group (46 and 54 years old, respectively). Seventy-one percent of patients in coexisting with endometriosis group was diagnosed as stage I ovarian cancer while patients without coexisting endometriosis were mainly in stage III disease (54%). Our finding showed the same direction with study of Ye et al. It was reported that ovarian cancer patients with endometriosis received a better optimal debulking surgery.

The present of endometriosis is associated with an increased risk of epithelial ovarian cancer. The odds ratios (OR), relative risks (RR) or standardized incidence ratios (SIR) have varied between 1.3 and 1.9 (Dunselman et al., 2014). The association of ovarian cancer and endometriosis is strongest (RR = 3) in cases of clear-cell and endometrioid subtype of epithelial ovarian cancer (Munksgaard and Blaakaer, 2011; Sayasneh et al., 2011) This finding supported the previous study.

Endometriosis had a significant effect on many aspects of women's lives such as economic burden, social, sexual relationships, work and study (De Graaff et al., 2013, Nnoaham et al., 2011). After menopause, the burden of endometriosis during reproductive life changed. Ovarian steroid hormones finished stimulating lesions and the major issue was due to the risk of malignant transformation (Heidemann et al., 2014).

Incidence of endometriosis might be increase nowadays. Endometriosis found about 50% in women with infertility (Eskenazi and Warner, 1997; Meuleman, et al., 2009) and up to 70 percent of adolescents with chronic pelvic pain (Berek et al., 2012). About ninety percent of reproductive women with chronic pelvic pain or infertility show some degree of endometriosis (Somigliana et al., 2006; Suh et al., 2013). The precise diagnosis is based on the histologic identification of endometriotic tissue. The measurement of serum CA 125 had limited potential to diagnose endometriosis. Currently, there are no known immunological biomarkers used in a non-invasive way for diagnosis of endometriosis (Dunselman et al., 2014). Many clinicians believe that surgical castration would lead to regression of remaining endometriotic lesions. However, hysterectomy with ovarian conservation was reported to have a 6-fold risk for development of recurrent pain and an 8.1-times greater risk of reoperation (Martin, 2006).

Endometriosis is a condition when found with ovarian cancer resulted in complication in surgery due to the adhesive problem. We found that optimal surgery rate in EAOC is higher than in non EAOC group. It looked like endometriosis presenting symptoms urged the patients to come to see the physician resulted in finding the underlying ovarian cancer at an earlier stage (45%).

In subgroup analysis of EAOC and non-EAOC in an

advance stage of disease, there is no significant different of suboptimal surgery between both groups. This is the same as previous reported by Kim et al., (2015) Younger age at diagnosis of disease, familial history of cancer and coexistence with endometriosis are factors associate to optimal surgery in our study. Age, performance status, nutrition, and obesity are additional risk that caused limitation of aggressive surgical cytoreduction in advanced stage ovarian cancer (Chang et al., 2015). Nulliparous woman mostly found in EAOC as in previous report. However, we found that smoker had 8 times more risk to develop EAOC which could not be explained in the pathophysiology of disease.

Limitation of this study may be from lack of some specific data due to the nature of retrospective study. Also, the small number of the participants may be another limitation.

In conclusion, EAOC found one-fifth in EOC. Age, familial history of cancer and coexistence with endometriosis are factors relate to suboptimal ovarian cancer surgery. Optimal surgery in EAOC patient is more common than in non-EAOC patient, but when subgroup analysis only of advance stage disease, the probability of optimal debulking surgery was not different between the two groups. Coexistence with endometriosis does not hinder the success of debulking surgery in advanced stage of ovarian cancer.

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