REVIEW ARTICLE

The association between endometriosis and survival outcomes of ovarian cancer: Evidence-based on a meta-analysis

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Abstract

Background: Although it is generally recognized that endometriosis was significantly associated with higher risk of ovarian cancer, the association between endometriosis and the cancer survival outcomes is still not clear. This meta-analysis aims to pool previous studies and to make an update estimate.

Methods: Relevant studies were searched among PubMed, Medline and Embase. Hazard ratio (HR) and the corresponding 95% confidence intervals (CI) of progression-free survival (PFS) and overall survival (OS) were pooled with generic inverse variance method. The proportion of the low stage and grade tumors (stage: Stage I and II among total; grade: Grade I among total) in endometriosis-associated ovarian cancer (EAOC) group and in non-EAOC group were assessed with odd ratio and the corresponding 95% CI.

Results: Endometriosis-associated ovarian cancer were significantly associated with higher rate of OS in crude analysis (HR: 0.74, 95% CI: 0.63-0.87, *P* = 0.0003). However, in most of the studies included, the OS benefit was not significant under multivariable survival analysis. EAOC patients generally had early-stage, low histological grade tumors and younger age compared with non-EAOC patients. No difference was observed in PFS between the two groups.

Conclusion: The OS benefits associated with endometriosis might be closely related to higher prevalence of patients diagnosed at early-stage and greater chance of receiving optimal cytoreductive surgery or chemotherapy. Endometriosis should not be viewed as an independent prognostic factor of ovarian cancer.

Key words: Endometriosis, meta-analysis, ovarian cancer, survival

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Introduction

Endometriosis is a common gynecologic disease characterized as ectopic growth of endometrial glands and stroma and with occurrence rate around 3% to 15% in premenopausal women.[1,2] This disease is usually caused by reflux of endometrial tissue through the fallopian tubes during menstruation to the abdomen, where it implants and grows. Altered immune response is also involved in the pathological process of endometriosis.[3] Endometriosis can result in chronic pain, adhesions, pelvic inflammation or even infertility. It is long been viewed as a risk factor for epithelial ovarian cancer.

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Invasive epithelial ovarian cancers usually include five major histological subgroups, including low or high-grade serous, mucinous, endometrioid and clear-cell.[4] These five subtypes have distinct molecular mechanisms and different pathological features.[5] One recent large multinational study demonstrated that endometriosis was associated with approximately 50% higher risk of certain histology subtypes of ovarian cancer, including clear-cell carcinoma (CCC), endometrioid carcinoma, and low-grade serous carcinoma.[6] Another recent meta-analysis also

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showed that endometriosis was significantly associated with higher risk of endometrioid and CCC.[7]

However, the association between endometriosis and ovarian cancer survival outcomes is still not clear. Previous studies reported conflicting results about the association. Some reported better survival in patients with endometriosis-associated ovarian cancer (EAOC) than in patients with non-EAOC.[8,9] However, this finding was not observed in some other studies.[10,11] Although Kim *et al*.'s meta-analysis explored endometriosis-associated progression outcomes, the small number of studies included did not provide sufficient statistical power.[7] In addition, some newly published studies based on large sample size offered new evidence about the association between endometriosis and ovarian cancer survival. Therefore, to better clarify this controversial issue, this study aims to pool previous studies and to make an update estimate.

Methods

Search strategy and selection criteria

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[12] Relevant studies were searched among PubMed, Medline and Embase between Jan 1990 and June 2014. The following terms and strategy were used for searching: ("ovarian tumor" OR "ovarian carcinoma" OR "ovarianneoplasm" OR "ovarian cancer") AND ("endometriosis") AND ("progression" OR "survival").

Studies meeting the following criteria at the same time were included in this meta-analysis: (1) Patients were diagnosed as epithelial ovarian cancer; (2) retrospective or prospective studies compared progression-free survival (PFS) or overall survival (OS) between EAOC and non-EAOC patients; (3) studies reported hazard ratio (HR) data of PFS and OS outcomes. Studies meeting any of the following criteria were excluded: (1) Case report, editorials or reviews; (2) detailed data could not be extracted. Reference lists of included studies and relevant meta-analysis or reviews were manually screened to avoid possible missing of qualified studies.

Data extraction

Two authors (BY and DW) independently performed data extraction. Discrepancies were resolved by referring to original studies with a third author (HC). The data extracted include first author, year of publication, study design, period of enrollment, sample size, assessment of endometriosis, histological subtype of ovarian cancer, adjuvant treatment, HR of PFS or OS (EAOC vs. non-EAOC patients), stage and grade information of the patients.

Data analysis

Review Manager 5.3 (RevMan 5.3; The Cochrane Collaboration) was used for statistical analysis. HRs and the corresponding 95% confidence intervals (CI) of PFS and OS were pooled with generic inverse variance method. When assessing OS, subgroup analysis was performed by stratifying subtypes of ovarian cancer. The proportion of the low stage and grade tumors (stage: Stage I and II among total; grade: grade I among total) in EAOC and non-EAOC group were assessed with odd ratio (OR) and the corresponding 95% CI. Between study heterogeneity was assessed by using Higgins I^2 statistic and Chi-square test.[13] $P < 0.1$ or $I^2 > 50\%$ indicate significant heterogeneity.[14] Fixed effects model was used for primary assessment. If no significant heterogeneity observed, fixed effects model was applied for final analysis. However, if significant heterogeneity observed, the source of the heterogeneity was further analyzed. If the studies were without significant clinical heterogeneity, random effects model was used for a secondary confirmatory analysis. When necessary, sensitivity analysis was conducted to test robustness of the findings. $P \leq 0.05$ of Z-test denoted statistical significance of pooled results. Publication bias was assessed by visual inspection of funnel plots of HR of PFS or OS. Asymmetrical distribution of the plots suggests high risk of publication bias.

Results

Literature search

Through searching in the databases and screening by using the criteria, a total of 13 studies were finally included in this meta-analysis.[8-11,15-23] The general searching and screening process was summarized in Figure 1. The key basic information of the 13 studies was presented in Table 1. All the studies were retrospective and were published between 1995 and 2014. These 13 studies involved 47,719 patients, with 4,768 EAOC and 42,951 non-EAOC cases. Except Melin's study, the remaining 12 studies all had endometriosis confirmed by histological examination. Three studies had age information

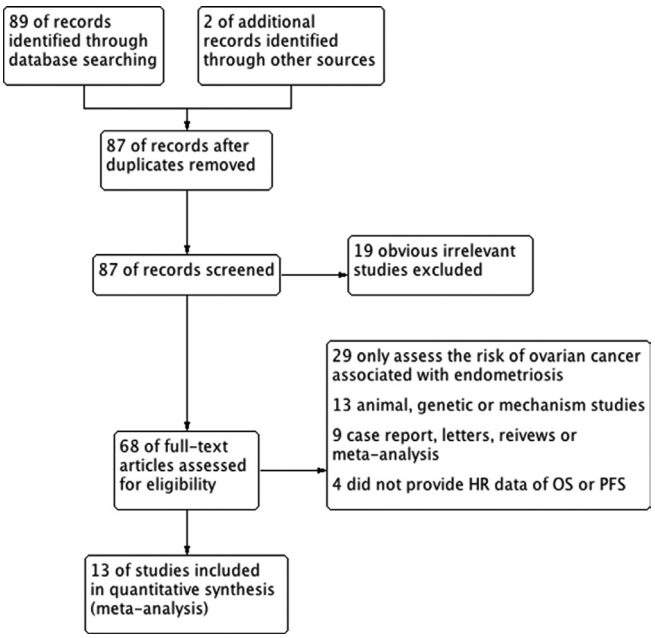

Figure 1: The searching and screening process

Table 1: The key characteristics of studies included

Study	Study design	Period of enrollment	Age (case vs. Control)	Endometriosis diagnosis	Histological subtype	FIGO stage	Number of patients		Survival outcome	Adjuvant treatment
							EAOC	Non-EAOC		
McMeekin *et al.* 1995	Retro	1979-1991	≥55, 32% versus 56%, *P*=0.039	Histology	Endometrioid, coexistent clear cell (15%)	I-IV	28	63	PFS, OS	PBC (66%), RT (4.4%), intraperitoneal ^{32}P (4.4%)
Komiyama *et al.* 1999	Retro	1984-1995	48.7 versus 53.5, *P*>0.05	Histology	Clear cell	I, III	19	28	OS	PBC
Erzen *et al.* 2001	Retro	1990-1999	54.5 versus 54.7 *P*>0.05	Histology	Serous, mucinous, endometrioid, clear cell and others	I-IV	58	232	OS	NS
Orezzoli *et al.* 2008	Retro	1975-2002	49 versus58, *P*=0.03	Histology	Clear cell	I-IV	41	43	PFS, OS	PBC (81%), RT (11.9%), CTWP (7.1%)
Garrett *et al.* 2013	Retro	2001-2009	NS	Histology	Clear cell, endometrioid, and mixed	I-IV	40	48	OS	PBC
Kumar *et al.* 2011	Retro	1992-2002	54 versus59, *P*=0.05	Histology	Serous, mucinous, endometrioid, clear cell	I-IV	42	184	OS	PBC
Melin *et al.* 2011	Retro	1969-2005	56.4 versus 56.7, *P*=0.06	Registration*	All histological types	I-IV	4,278	41,831	OS	NS
Cuff and Longacre 2012	Retro	N.S.	NS	Histology	Endometrioid, clear cell, mixed	I-IV	60	80	PFS	NS
Katagiri *et al.* 2012	Retro	N.S.	NS	Histology	Clear cell	I-IV	28	32	PFS, OS	PBC
Noli *et al.* 2013	Retro	1990-2010	51.4 versus 54.3, *P*=0.31	Histology	Clear cell, endometrioid	I-IV	36	77	OS	NS
Wang *et al.* 2013	Retro	2000-2012	45.8 versus 51.2, *P*=0.028	Histology	endometrioid, mixed with clear cell	I-IV	32	156	PFS	NS
Shuang 2014	Retro	2000-2012	46 versus54, *P*<0.01	Histology	Clear cell	I-IV	79	131	PFS, OS	PBC
Scarfone *et al.* 2014	Retro	1990-2012	51.4 versus 58.4, *P*=0.02	Histology	Clear cell, mixed	I-IV	27	46	OS	NS

*Hospital discharge diagnosis identified from the National Swedish patient Register. EAOC=Endometriosis-associated ovarian cancer; FIGO=International Federation of Gynecology and Obstetrics; OS=Overall survival; PFS=Progression-free survival. PBC=Platinum-based chemotherapy; RT=Radiotherapy; CTWP=Chemotherapy without platinum agents; NS=Not stated

unavailable.[9,10,24] Among the remaining ten studies, 6 reported significantly lower age of EAOC patients than non-EAOC patients.[8,11,15,18,22,23] The studies varied in subtypes of ovarian cancers. Four studies only involved patients with clear-cell cancer,[8,16,22,24] while the remaining nine studies involved patients with different subtypes or mixed cancers. Most the studies had patients with cancer stages ranging from I to IV. Four studies reported both HR of PFS and OS,[8,15,22,24] while seven studies only reported HR of OS[9,16-19,21,23] and two studies only reported HR of PFS.[10,11] The detailed HR data of PFS and OS, and stage and grade information of the patients were extracted and summarized in Table 2.

The association between endometriosis and progression-free survival

Six studies including 773 patients (268 in EAOC and 505 in non-EAOC group) reported the association between endometriosis and PFS. Meta-analysis showed that PFS was similar between EAOC and non-EAOC patients (HR: 0.87, 95% CI: 0.65-1.16, $P = 0.33$) [Figure 2a]. No significant heterogeneity was observed ($P = 0.13$, $I^2 = 41\%$) [Figure 2a]. Excluding any one of the six studies could not change the trend. Thus, this finding is highly robust.

The association between endometriosis and overall survival

Eleven studies including 47,391 patients (4,676 in EAOC and 42,715 in non-EAOC group) reported the association between endometriosis and OS. In general, meta-analysis showed that EAOC group had significantly higher OS rate than non-EAOC group (HR: 0.74, 95% CI: 0.63-0.87, $P = 0.0003$) [Figure 2b]. No significant heterogeneity was observed ($P = 0.51$, $I^2 = 0\%$). Subgroup analysis showed that the trend of endometriosis-associated higher OS rate was similar in clear-cell ovarian cancer subgroup (HR: 0.72, 95% CI: 0.48-1.06, $P = 0.10$) and in mixed subtype of ovarian cancer subgroup (HR: 0.75, 95% CI: 0.63-0.89, $P = 0.001$) [Figure 2b]. However, except Erzen *et al.*'s study,[17] the remaining studies all reported no significant association between endometriosis and OS under multivariate analyses ($P > 0.05$) [Table 2]. Thus, there might be some confounding factors.

The association between endometriosis and tumor stage and grade

Meta-analysis showed that endometriosis was significantly associated with lower stage and grade of ovarian cancer. Nine studies reported detailed International Federation of Gynecology and Obstetrics (FIGO) stage information of EAOC and Non-EAOC group. The proportions of low stage tumors (I and II) in these two groups were 265/359 (73.8%) and 403/964 (41.8%) respectively (OR: 4.13, 95% CI: 3.11-5.47, $P < 0.00001$, $I^2 = 43\%$) [Figure 3a]. Five studies reported detailed grade information in these two groups. The proportions of low-grade tumor (I) in these two groups were

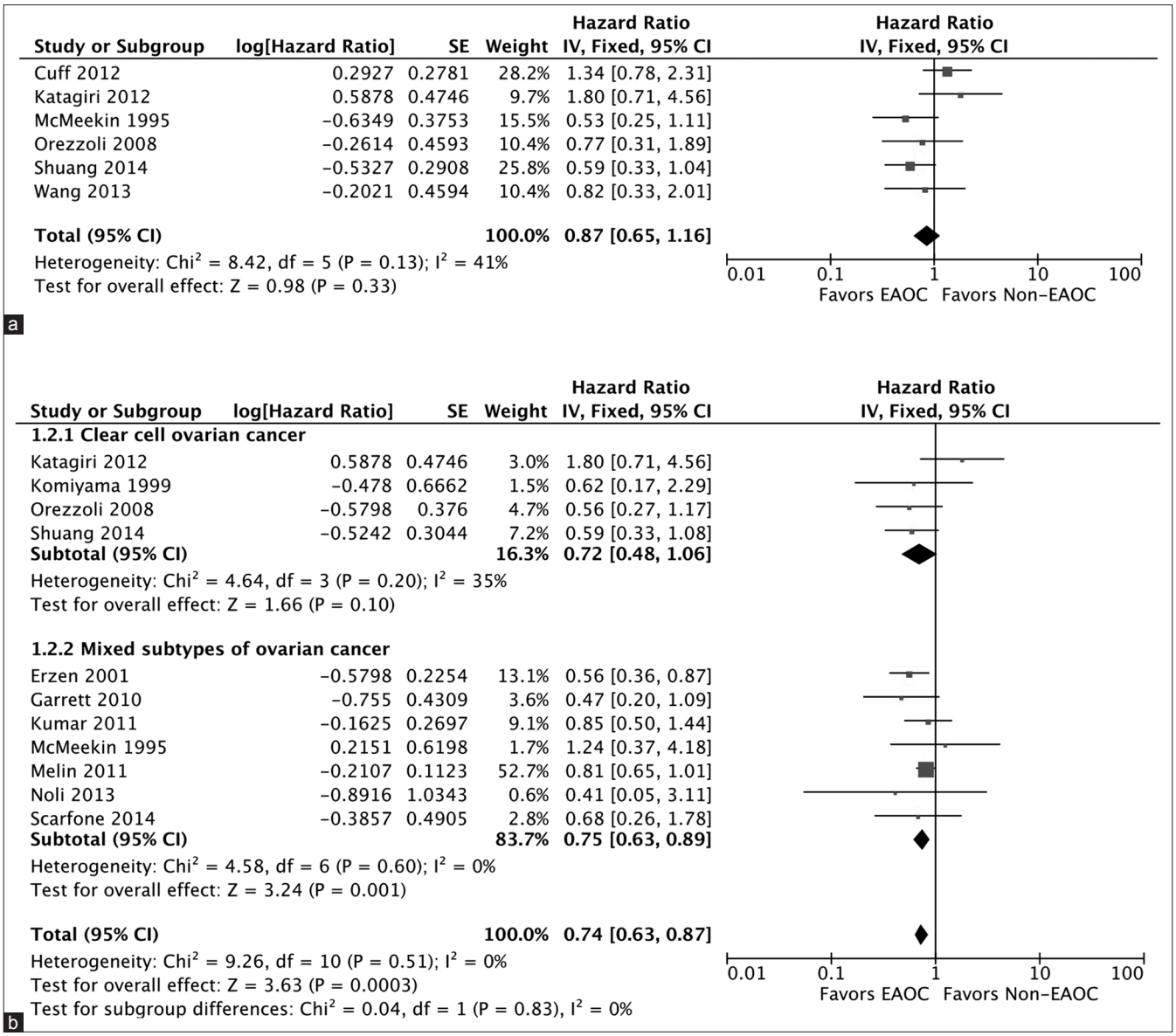

Figure 2: The association between endometriosis and survival outcomes (a) The association between endometriosis and progression-free survival. (b) The association between endometriosis and overall survival

61/183 (33.3%) and 129/669 (19.3%) respectively (OR: 2.31, 95% CI: 1.58-3.36, $P < 0.0001$, $I^2 = 38\%$) [Figure 3b].

Publication bias

Since 12 out of 13 studies reported outcome of OS, funnel plots of HR of OS were used to assess publication bias. The plots demonstrate nearly symmetric distribution at the top of the funnel, suggesting a relatively low risk of publication bias [Figure 4].

Discussion

Previous studies found that approximately 1/3 of clear-cell or endometrioid ovarian cancers may arise from endometriosis.[25] Different types of ovarian cancer arising from endometriosis might have distinct mechanisms and might even arise from distinct types of endometriosis with different cells of origin. Previous studies observed altered oncogene or anti-oncogene in the malignant transformation of endometriosis, such as p53 alterations, PTEN silencing and K-ras mutations.[27] It is hypothesized that malignant transformation of benign endometriosis might be an origin of ovarian cancer.[26] Considering the different genetic and nongenetic origins of EAOCs when compared to non-EAOCs, there might also be differences in OS. Although the association between endometriosis and ovarian cancer risk is well recognized in previous studies, its association with cancer survival is still conflicting.

This meta-analysis showed that EAOC was significantly associated with higher OS rate than non-EAOC in crude analysis, but no difference was observed in PFS.

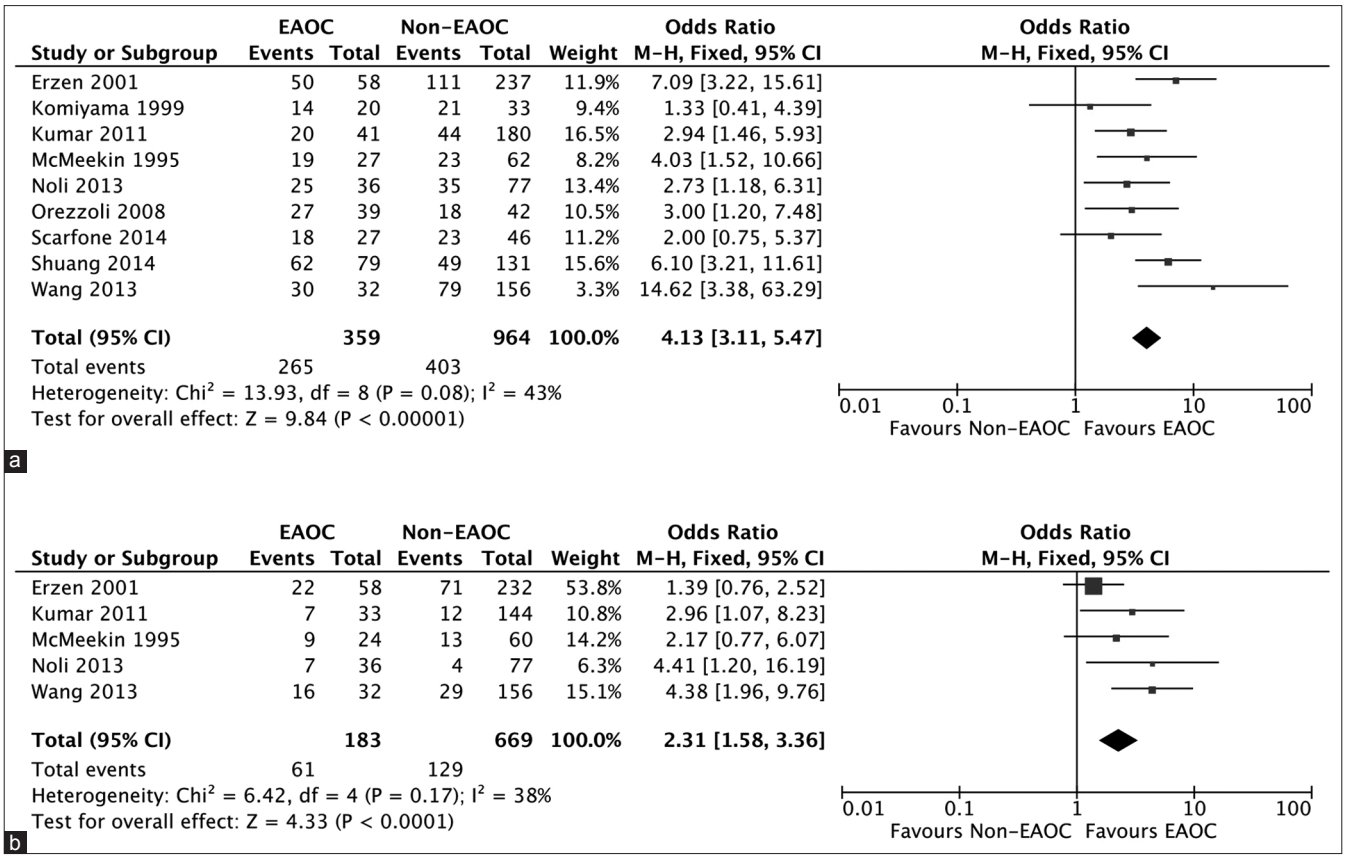

Figure 3: Meta-analysis of the proportion of low stage and grade tumors in endometriosis-associated ovarian cancer (EAOC) and non-EAOC patients. (a) The proportion of low stage tumors in EAOC and non-EAOC patients. (b) The proportion of low-grade tumors in EAOC and non-EAOC patients

Table 2: Original HR of OS and PFS, stage and grade information

Study	OS		PFS		FIGO stage				Grade			
	HR (95% CI)	*P*	HR (95% CI)	*P*	EAOC		Non-EAOC		EAOC		Non-EAOC	
					I, II	III, IV	I, II	III, IV	I	II, III	I	II, III
McMeekin *et al*. 1995	1.24 (0.37, 4.18)	0.73	0.53 (0.25, 1.11)	0.09	19	8	23	39	9	15	13	47
Komiyama *et al*. 1998	0.62 (0.17, 2.29)	0.47	-	-	14	6	21	12	-	-	-	-
Erzen *et al*. 2001	0.56 (0.36, 0.87)	0.01	-	-	50	8	111	126	22	36	71	161
Orezzoli *et al*. 2008	0.56 (0.27, 1.17)	0.12	0.77 (0.31, 1.89)	0.57	27	12	18	24	-	-	-	-
Garrett *et al*. 2010	0.47 (0.20, 1.09)	0.08	-	-	-	-	-	-	-	-	-	-
Kumar *et al*. 2011	0.85 (0.50, 1.44)	0.55	-	-	20	21	44	136	7	26	12	132
Melin *et al*. 2011	0.81 (0.65, 1.01)	0.06	-	-	-	-	-	-	-	-	-	-
Cuff and Longacre 2012	1.80 (0.71, 4.56)	0.22	1.80 (0.71, 4.56)	0.22	-	-	-	-	-	-	-	-
Katagiri *et al*. 2012	-	-	1.34 (0.78, 2.31)	0.29	-	-	-	-	-	-	-	-
Noli *et al*. 2013	0.41 (0.05, 3.11)	0.39	-	-	25	11	35	42	7	29	4	73
Wang *et al*. 2013	-	-	0.82 (0.33, 2.01)	0.66	30	2	79	77	16	16	29	127
Shuang 2014	0.59 (0.33, 1.08)	0.09	0.59 (0.33, 1.04)	0.07	62	17	49	82	-	-	-	-
Scarfone *et al*. 2014	0.68 (0.26, 1.78)	0.43	-	-	18	9	23	23	-	-	-	-

HR=Hazard ratio; CI=Confidence interval; OS=Overall survival; PFS=Progression free survival; EAOC=Endometriosis-associated ovarian cancer; -=Not available; FIGO=International Federation of Gynecology and Obstetrics

However, in most of the studies included, the OS benefit was not significant under multivariable survival analysis, suggesting there were some confounding factors. This study further confirmed a trend that EAOC patients generally had early-stage and low histological grade tumors compared with non-EAOC patients. In addition, this study also observed significantly lower age of EAOC patients than the non-EAOC patients in most of the studies. Therefore, this might lead to a hypothesis that the OS benefits associated with endometriosis might

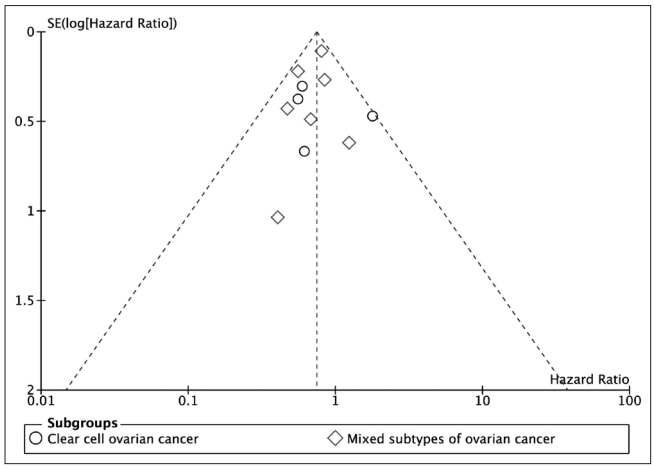

Figure 4: Funnel plot analysis of publication bias

be closely related to higher prevalence of patients diagnosed at early-stage and greater chance of receiving optimal cytoreductive surgery or chemotherapy. Due to endometriosis, patients usually had some symptoms such dyspareunia, dysmenorrhea, and/or pelvic mass and thus went to hospital for gynecologial examination, leading to high possibility of ovarian cancer diagnosed at an early-stage. Actually, this hypothesis is supported by some previous retrospective studies.[28,29] In addition, it is still unclear whether EAOC is caused by malignant transformation in endometriosis or endometriosis and ovarian cancer simply coexist.[9] Therefore, endometriosis should not be viewed as an independent prognostic factor.

Some studies indicated that in EAOC patients, the FIGO stage at diagnosis was a natural consequence of the symptomatic character of the coexisting condition.[1] For example, abdominal or pelvic pain is the most common presenting sign/symptom in EAOC patients and adnexal mass was found in about 2/3 of the EAOC patients.[8] In addition, 2/3 of EAOC patients also presented ovarian cancer symptoms such as progressive abdominal girth, bloating, distension, lower extremity swelling and alterations in bowel function. Therefore, in the clinical settings, once patients develop symptoms and are diagnosed with endometriosis they should be observed closely because they could be at risk for malignancy.

This study also had several limitations. First, the studies included are all retrospective in nature and thus have different definitions of EAOC. Some studies defined EAOC as transition of benign to malignant tissue, while some only described the presence of endometriosis in nearby tissue. The former definition might exclude cases in areas where were not sampled or the transformation had developed to a level where malignant tissue had overridden the benign tissue. However, the latter definition may increase the risk of overdiagnosis, especially when endometriosis and cancer simply coexist. Secondly, in different studies, the adjuvant treatment was different. Even in one study, the therapy in EAOC or non-EAOC group was also different. For example, in Orezzoli *et al*.'s study,[8] 60% EAOC patients received platinum-based regimens in combination with taxanes, while the proportion in non-EAOC group was only 39%. Adjuvant therapy is also an important factor affecting survival. This variance might lead to bias when assessing survival outcome.

Conclusion

Although EAOC was associated with significantly higher OS rate than non-EAOC, the benefit was generally not significant under multivariable survival analysis. EAOC patients were younger at diagnosis and had early-stage and low histological grade tumors compared with non-EAOC patients. Thus, the OS benefits associated with endometriosis might be closely related to higher prevalence of patients diagnosed at early-stage and greater chance of receiving optimal cytoreductive surgery or chemotherapy. Endometriosis should not be viewed as an independent prognostic factor.

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