Keywords: endometriosis; ovarian cancer; risk; prognosis; meta-analysis

Risk and prognosis of ovarian cancer in women with endometriosis: a meta-analysis

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Background: The risk and prognosis of ovarian cancer have not been well established in women with endometriosis. Thus, we investigated the impact of endometriosis on the risk and prognosis for ovarian cancer, and evaluated clinicopathologic characteristics of endometriosis-associated ovarian cancer (EAOC) in comparison with non-EAOC.

Methods: After we searched an electronic search to identify relevant studies published online between January 1990 and December 2012, we found 20 case–control and 15 cohort studies including 444 255 patients from 1 625 potentially relevant studies. In the meta-analysis, ovarian cancer risk by endometriosis and clinicopathologic characteristics were evaluated using risk ratio (RR) or standard incidence ratio (SIR), and prognosis was investigated using hazard ratio (HR) with 95% confidence interval (CI). Heterogeneity was evaluated using Higgins I^2 to select fixed-effect ($I^2 \leq 50\%$) or random effects models ($I^2 > 50\%$), and found no publication bias using funnel plots with Egger's test ($P > 0.05$). Furthermore, we performed subgroup analyses based on study design, assessment of endometriosis, histology, disease status, quality of study and adjustment for potential confounding factors to minimise bias.

Results: Endometriosis increased ovarian cancer risk in case–control or two-arm cohort studies (RR, 1.265; 95% CI, 1.214–1.318) and single-arm cohort studies (SIR, 1.797; 95% CI, 1.276–2.531), which were similar in subgroup analyses. Although progression-free survival was not different between EAOC and non-EAOC (HR, 1.023; 95% CI, 0.712–1.470), EAOC was associated with better overall survival than non-EAOC in crude analyses (HR, 0.778; 95% CI, 0.655–0.925). However, progression-free survival and overall survival were not different between the two groups in subgroup analyses. Stage I–II disease, grade 1 disease and nulliparity were more common in EAOC (RRs, 1.959, 1.319 and 1.327; 95% CIs, 1.367–2.807, 1.149–1.514 and 1.245–1.415), whereas probability of optimal debulking surgery was not different between the two groups (RR, 1.403; 95% CI, 0.915–2.152). Furthermore, endometrioid and clear cell carcinomas were more common in EAOC (RRs, 1.759 and 2.606; 95% CIs, 1.551–1.995 and 2.225–3.053), whereas serous carcinoma was less frequent in EAOC than in non-EAOC (RR, 0.733; 95% CI, 0.617–0.871), and there was no difference in the risk of mucinous carcinoma between the two groups (RR, 0.805; 95% CI, 0.584–1.109). These clinicopathologic characteristics were also similar in subgroup analyses.

Conclusions: Endometriosis is strongly associated with the increased risk of ovarian cancer, and EAOC shows favourable characteristics including early-stage disease, low-grade disease and a specific histology such as endometrioid or clear cell carcinoma. However, endometriosis may not affect disease progression after the onset of ovarian cancer.

Endometriosis is a common gynecologic disease that affects 3–15% of premenopausal women and 3–5% of postmenopausal women (Del Carmen *et al*, 2003). Furthermore, up to 90% of reproductive

women with chronic pelvic pain or infertility show some degree of endometriosis (Somigliana *et al*, 2006; Suh *et al*, 2013). In spite of a common disease in women, the aetiology of endometriosis is still

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uncertain (Bulun, 2009). Moreover, endometriosis is considered as a benign condition and it does not result in a catabolic state like a malignancy, whereas it shares common characteristics of ovarian cancer such as tissue invasion, unrestrained growth, angiogenesis and a decrease in the number of cells undergoing apoptosis.

When compared with other female malignancies such as breast, lung and colon cancers, the incidence of ovarian cancer is relatively low (5.0–9.4 per 100 000 women), and it shows the cumulative risk of 0.5–1.0% globally (Jemal *et al*, 2011). However, ovarian cancer is known to develop in 0.3–1.6% of women with endometriosis (Mostoufzadeh and Scully, 1980; Seidman, 1996; Swiersz, 2002), and endometriosis is observed in 4–29% of patients with ovarian cancer (Somigliana *et al*, 2006), which suggest the association between endometriosis and ovarian cancer. In addition, the malignant transformation of endometriosis by genetic mutations and altered microenvironments has been suggested in spite of the lack of precise mechanisms (Yamaguchi *et al*, 2008).

Epidemiologically, endometriosis has been reported to increase the risk of ovarian cancer in some studies (Ness *et al*, 2000, 2002; Borgfeldt and Andolf, 2004; Modugno *et al*, 2004; Pearce *et al*,

2012) that suggest the possibility that endometriosis-associated ovarian cancer (EAOC) may be developed through different mechanisms in comparison with non-EAOC. However, the increased risk was not noted in other studies (Royar *et al*, 2001; Olson *et al*, 2002; Brinton *et al*, 2004; Glud *et al*, 2004; Terry *et al*, 2005; Risch *et al*, 2006; Cunningham *et al*, 2009; Bodmer *et al*, 2011; Ness *et al*, 2011). Moreover, the difference in prognosis between EAOC and non-EAOC patients is still not clear. Some studies have shown better survival in patients with EAOC (Erzen *et al*, 2001; Melin *et al*, 2011), whereas it was not different between the two groups in other studies (McMeekin *et al*, 1995; Komiyama *et al*, 1999; Orezza *et al*, 2008; Kumar *et al*, 2011; Cuff and Longacre, 2012; Katagiri *et al*, 2012). For explaining better prognosis in patients with EAOC, some investigators have reported that they may have favourable characteristics such as young age, early-stage disease, a specific histology such as endometrioid or clear cell carcinoma, low-grade disease and an increase of probability of optimal debulking surgery (McMeekin *et al*, 1995; Ziogas *et al*, 2000; Erzen *et al*, 2001; Orezza *et al*, 2008; Rossing *et al*, 2008; Kumar *et al*, 2011; Wang *et al*, 2013), whereas these

Figure 1. Forest plots for (A) risk ratio with 95% CI in case-control or two-arm cohort studies, and (B) SIR with 95% CI in single-arm cohort studies to assess an increased risk of ovarian cancer by endometriosis.

findings were not identified in other relevant studies (Komiya *et al*, 1999; Lim *et al*, 2009; Boyraz *et al*, 2013).

Some pooled analyses or systematic reviews using a small number of case-control or cohort studies suggested the impact of endometriosis on ovarian cancer risk and prognosis (Ness *et al*, 2002; Modugno *et al*, 2004; Sayasneh *et al*, 2011; Pearce *et al*, 2012), and a recent meta-analysis showed an increased risk of ovarian cancer with histologically verified endometriosis (Heidemann *et al*, 2014). However, a comprehensive attempt is needed for quantifying ovarian cancer risk in women with endometriosis, and for clarifying prognosis and clinicopathologic characteristics of EAO when we consider that endometriosis was determined by various methods including self-report, registration from databases and histology in many relevant studies. With the aim of disentangling these intriguing and controversial issues, we performed a meta-analysis using the largest number of relevant studies published up to now.

MATERIALS AND METHODS

Search strategy and selection criteria. The study was conducted in line with the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati *et al*, 2009). For the meta-analysis, we searched PubMed, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library for relevant studies published

online between January 1990 and December 2012. The search terms used were the following: 'ovarian tumor and endometriosis', 'ovarian neoplasm and endometriosis', 'ovarian carcinoma and endometriosis' and 'ovarian cancer and endometriosis'.

We included relevant studies that met the following criteria: (1) epithelial ovarian cancer; (2) case-control or two-arm cohort studies comparing ovarian cancer risk between women with endometriosis and those without endometriosis; (3) single-arm cohort studies comparing ovarian cancer risk between observed and expected events of ovarian cancer in only women with endometriosis; and (4) studies comparing progression-free survival, overall survival and clinicopathologic characteristics between EAO and non-EAO patients. However, we excluded studies as follows: (1) review articles; (2) case reports or editorials or letters to the editor not including original data; (3) studies not meeting the selection criteria; and (4) non-English literature.

Selection of studies. Two of the authors (HSK and HHC) independently evaluated potential eligibility of all studies retrieved from the database according to the predetermined selection and exclusion criteria, and the third author (YSS) resolved disagreement between the two authors after discussion. As a result, a total of 1625 studies were identified, and we excluded 89 duplicates and an additional 624 including reviews ($n=294$), case reports ($n=157$), non-English literature ($n=145$), editorials or letters to the editor ($n=25$), and relevant pooled analyses where we could not obtain individual data from each study, and data from some studies overlapped with those included in the meta-analysis ($n=3$).

Table 1. Subgroup analyses for assessing an increased risk of ovarian cancer by endometriosis

				Heterogeneity		
Category	No. of studies with references	RR or SIR	95% CI	P	I ²	Model used
Case-control or two-arm cohort studies						
Study design						
Case-control	18	1.253	1.202–1.307	0.994	0	Fixed effect
Cohort	3	1.610	1.306–1.985	0.435	0	Fixed effect
Assessment of endometriosis						
Self-report	16	1.252	1.192–1.314	0.976	0	Fixed effect
Histology	5	1.299	1.203–1.401	0.200	33.149	Fixed effect
Quality of study (NOS)						
≥7	16	1.265	1.208–1.324	0.738	0	Fixed effect
<7	5	1.266	1.155–1.388	0.801	0	Fixed effect
Adjustment for potential confounding factors						
Three factors ^a	17	1.270	1.211–1.332	0.760	0	Fixed effect
Eight factors ^b	14	1.254	1.192–1.319	0.961	0	Fixed effect
Single-arm cohort studies						
Assessment of endometriosis						
Histology	4	1.463	1.233–1.749	0.559	0	Fixed effect
Adjustment for potential confounding factors						
Two factors ^c	4	1.507	1.255–1.810	0.023	68.416	Random effects
Three factors ^d	3	1.482	1.231–1.785	0.014	76.514	Random effects

Abbreviations: CI = confidence interval; NOS = Newcastle–Ottawa Scale; RR = risk ratio; SIR = standard incidence ratio.

^aAdjusted for age, history of tubal ligation, and parity.

^bAge, body mass index, breastfeeding, family history of ovarian cancer, history of tubal ligation, parity, race, and use of oral contraceptive.

^cAge and calendar year at entry.

^dAge, calendar year at entry, and duration of follow-up.

(Ness *et al*, 2002; Modugno *et al*, 2004; Pearce *et al*, 2012). In addition, we excluded 860 studies because of non-ovarian cancer ($n = 640$), no endometriosis ($n = 87$) and no data about clinico-pathologic characteristics, ovarian cancer risk or prognosis ($n = 133$). Furthermore, 17 were also excluded because of no appropriate comparator ($n = 16$), and not enough data to calculate survival ($n = 1$). Finally, 20 case-control (Ness *et al*, 2000; Ziogas *et al*, 2000; Royar *et al*, 2001; Erzen *et al*, 2001; Borgfeldt and Andolf, 2004; Glud *et al*, 2004; Pike *et al*, 2004; Terry *et al*, 2005; Risch *et al*, 2006; Merritt *et al*, 2008; Moorman *et al*, 2008; Rossing *et al*, 2008; Cunningham *et al*, 2009; Wu *et al*, 2009; Lurie *et al*, 2010; Balogun *et al*, 2011; Bodmer *et al*, 2011; Kumar *et al*, 2011; Ness *et al*, 2011; Vitonis *et al*, 2011) and 15 cohort studies (McMeekin *et al*, 1995; Brinton *et al*, 1997; Komiyama *et al*, 1999; Olson *et al*, 2002; Brinton *et al*, 2004; Brinton *et al*, 2005; Melin *et al*, 2006; Kobayashi *et al*, 2007; Melin *et al*, 2007; Orezzaoli *et al*, 2008; Aris, 2010; Melin *et al*, 2011; Cuff and Longacre, 2012; Katagiri *et al*, 2012; Wang *et al*, 2013; Supplementary Figure 1).

Data extraction. Data extraction was also performed by the two authors (HSK and THK), and any discrepancies were addressed by a joint reevaluation of the article with the third author (YSS). The following data were independently extracted from each study for the meta-analysis: the first author; period of enrollment; study design; assessment of endometriosis; age; numbers of women with endometriosis and those without endometriosis in case-control or two-arm cohort studies; numbers of observed and expected events of ovarian cancer, sample size and a number of person-years in single-arm cohort studies; adjustment for potential confounding factors; the International Federation of Gynecology and Obstetrics (FIGO) stage; grade; nulliparity; optimal debulking surgery; histology; numbers of EAOc and non-EAOc patients; and

progression-free survival or overall survival. When there was a lack of the relevant data in some studies, we could obtain the formation from some authors whom we contacted or databases suggested from systematic reviews or pooled analyses (Ness *et al*, 2002; Modugno *et al*, 2004; Sayasneh *et al*, 2011; Pearce *et al*, 2012).

Quality assessment. We assessed the quality of each study using the Newcastle–Ottawa Scale (NOS) for included case-control and cohort studies (Wells *et al*). The NOS consists of three parameters of quality: selection, comparability and exposure (for a case-control study) or outcome (for a cohort study). It assigns a maximum of four points for selection, two points for comparability and three points for exposure or outcome. In the current study, we considered a study with NOS score ≥ 7 as a high-quality study because it has been used as the criteria of high-quality study in spite of no standard criteria (Myung *et al*, 2009; Castillo *et al*, 2011). In case-control studies, 15 (75%) were of high quality with an average NOS score of 6.9 (Supplementary Table 1), and 10 (66.6%) showed high quality with an average NOS score of 7.6 in cohort studies (Supplementary Table 2).

Statistical analyses. Dichotomous data eligible in each study were shown as a risk ratio (RR) with its 95% confidence interval (CI) in case-control or two-arm cohort studies. In the meta-analysis using single-arm cohort studies, standard incidence ratio (SIR), which was computed as the observed number of events divided by the expected number of events in only women with endometriosis, and 95% CI were calculated. Moreover, we performed survival analyses using the statistical procedure described by Tierney *et al* (2007). Heterogeneity was assessed using Higgins I^2 that measures the percentage of total variation across studies that is due to heterogeneity rather than chance (Higgins *et al*, 2003). An $I^2 > 50\%$

Figure 2. Forest plots for HRs and 95% CIs to compare (A) progression-free survival and (B) overall survival between EAOc and non-EAOc.

was considered to represent substantial heterogeneity, and we used the random effects model using the DerSimonian and Laird method. On the other hand, the fixed effect model using the Mantel–Haenszel method was used in this meta-analysis when the I^2 was $\leq 50\%$ because it indicated no heterogeneity.

For identifying publication bias, funnel plots were represented that were scatter plots of hazard ratios (HRs) or RRs or SIRs of individual studies on the X axis against the standard error of the log HR or log RR or log SIR of each study on the Y axis. As a result, all funnel plots resembled symmetric inverter funnels that suggested no publication bias in this meta-analysis. Furthermore, we also found no publication bias using Egger's test ($P > 0.05$) (Supplementary Figure 2). For this analysis, we used Comprehensive Meta-analysis Version 2.0 (Biostat Inc., Englewood, NJ, USA), and a $P < 0.05$ was considered statistically significant.

RESULTS

Impact of endometriosis on ovarian cancer risk. Supplementary Tables 3 and 4 show general characteristics of 18 case–control or three two-arm cohort studies including 314 421 women with or without endometriosis, and five single-arm cohort studies including 79 388 women with endometriosis. Potential confounding factors including age, parity, history of tubal ligation and use of oral contraceptive were adjusted in most of studies. As a result, ovarian cancer risk increased in women with endometriosis when compared with those without endometriosis in case–control or two-arm cohort studies (RR, 1.265; 95% CI, 1.214–1.318;

Figure 1A), and single-arm cohort studies (SIR, 1.797; 95% CI, 1.276–2.531; Figure 1B). When we performed subgroup analyses based on study design, assessment of endometriosis, quality of study and adjustment for potential confounding factors, all results also showed that endometriosis was associated with an increased risk of ovarian cancer (Table 1).

Impact of endometriosis on ovarian cancer prognosis. Next, we compared progression-free survival and overall survival between EAO and non-EAO patients in eight relevant studies with NOS score ≥ 7 that included 47 047 patients, the characteristics of which are summarised in Supplementary Table 5. In most of the studies, patients with EAO were relatively young in comparison with those with non-EAO. In terms of survival, there was no difference in progression-free survival between EAO and non-EAO (HR, 1.023; 95% CI, 0.712–1.470; Figure 2A), whereas EAO was associated with a better overall survival than non-EAO in crude analyses (HR, 0.778; 95% CI, 0.655–0.925; Figure 2B). However, there were no differences in progression-free survival and overall survival between EAO and non-EAO in subgroup analyses based on histology, assessment of endometriosis, FIGO stage and adjustment for potential confounding factors (Table 2).

Clinicopathologic characteristics in endometriosis-associated ovarian cancer. Finally, we evaluated clinicopathologic characteristics between EAO and non-EAO in six cohort studies including 46 563 patients and 15 case–control studies including 8417 patients. General characteristics are depicted in Supplementary Table 6. In crude analyses, FIGO stage I–II disease (RR, 1.959; 95% CI, 1.367–2.807; Figure 3A), grade 1 disease (RR, 1.319; 95% CI, 1.149–1.514; Figure 3B) and nulliparity (RR, 1.327; 95% CI, 1.245–1.415; Figure 3C) were more

Table 2. Subgroup analyses for assessing prognosis of endometriosis-associated ovarian cancer

				Heterogeneity		
Category	No. of studies with references	HR	95% CI	P	I ²	Model used
Progression-free survival						
Histology						
Clear cell carcinoma	3	0.835	0.531–1.312	0.150	47.280	Fixed effect
Adjustment for potential confounding factors						
Age	3	1.263	0.832–1.916	0.415	0	Fixed effect
Age, optimal debulking surgery	2	1.155	0.725–1.842	0.303	5.928	Fixed effect
Overall survival						
Assessment of endometriosis						
Histology	6	0.730	0.553–0.964	0.251	24.352	Fixed effect
FIGO stage						
Early stage (I–II)	3	0.753	0.494–1.147	0.979	0	Fixed effect
Advanced stage (III–IV)	3	0.908	0.590–1.397	0.977	0	Fixed effect
Histology						
Clear cell carcinoma	3	0.820	0.352–1.911	0.098	56.856	Random effects
Adjustment for potential confounding factors						
Age	6	0.771	0.647–0.918	0.272	21.432	Fixed effect
Age, grade	4	0.840	0.578–1.221	0.267	24.086	Fixed effect
Age, grade, platinum-based chemotherapy	3	0.966	0.626–1.491	0.303	16.295	Fixed effect
Abbreviations: CI = confidence interval; FIGO = International Federation of Gynecology and Obstetrics; HR = hazard ratio.						

common in EAOC, whereas there was no difference in probability of optimal debulking surgery between EAOC and non-EAOC (RR, 1.403; 95% CI, 0.915–2.152; Figure 3D). In subgroup analyses according to study design, assessment of endometriosis, quality of study and adjustment for potential confounding factors, the results were similar except no difference in grade 1 disease in studies with NOS score <7 (RR, 1.087; 95% CI, 0.518–2.280; Table 3).

In terms of histology, crude analyses showed that serous carcinomas were less frequent in EAOC than in non-EAOC (RR, 0.733; 95% CI, 0.617–0.871; Figure 3E), and there was no difference in the risk of mucinous carcinomas between the two groups (RR, 0.805; 95% CI, 0.584–1.109; Figure 3F), whereas endometrioid carcinomas (RR, 1.759; 95% CI, 1.551–1.995; Figure 3G) and clear cell carcinomas (RR, 2.606; 95% CIs, 2.225–3.053; Figure 3H) were more common in

Figure 3. Forest plots for RRs and 95% CIs to compare clinicopathologic characteristics including (A) stage I–II disease, (B) grade 1 disease, (C) nulliparity, (D) probability of optimal debulking surgery, and (E) serous, (F) mucinous, (G) endometrioid, and (H) clear cell carcinomas between EAOC and non-EAOC.

EAOC than in non-EAOC. These findings were more definite in subgroup analyses based on study design, quality of study, assessment of endometriosis and adjustment for potential confounding factors except no difference in the risk of serous carcinoma in studies where endometriosis was assessed with histology (RR, 0.408; 95% CI, 0.064–2.585; Table 4).

DISCUSSION

Recent studies suggest the possibility that genetic and nongenetic factors potentially contribute to the neoplastic progression of endometriosis, where the following five typical factors have been suggested to increase ovarian cancer risk by endometriosis: atypical

Figure 3. (Continued)

endometriosis as a precursor of malignancy; genetic alteration in endometrial tissues; heme or free iron-induced oxidative stress; chronic inflammation; and steroid hormones including oestrogen and progesterone (Del Carmen *et al*, 2003; Somigliana *et al*, 2006; Mandai *et al*, 2009; Kokcu, 2011; Munksgaard and Blaakaer, 2012). For supporting the possibility of the malignant transformation of endometriosis, a recent pooled analysis has reported that the association of a history of ES with an increased risk of ovarian cancer may be clear, in particular, for low-grade serous, endometrioid and clear cell carcinoma, showing the consistency with laboratory evidence of related molecular and genetic alterations (Pearce *et al*, 2012).

However, relevant reviews and pooled analyses have some limitations as follows: first, some case-control or cohort studies include only women with moderate or severe endometriosis that thereby can overestimate ovarian cancer risk. Second, definite information about well-known preventive factors of ovarian cancer such as duration of hormonal agent use, infertility and gynaecologic treatment are missing, although potential confounding factors have been reported to be controlled. Third, hospital- or community-based control groups and interview or self-report without medical records can act as selection or recall bias. Furthermore,

different regimen of adjuvant chemotherapy after surgery can also be a limitation for comparing prognosis between EAO and non-EAO patients.

Although the meta-analysis could not overcome these limitations completely, and most of include studies did not show the definite relation between ovarian cancer and endometriosis in spite of the suggested criteria for the diagnosis of ovarian cancer arising from endometriosis (Sampson, 1925), it has major advantages as follows. We included the greatest number of relevant studies, and performed subgroup analyses according to study design, assessment of endometriosis, histology, FIGO stage, quality of study and adjustment for potential confounding factors to minimise bias. As a result, we obtained the following meaningful results in the meta-analysis.

First, endometriosis increased ovarian cancer risk by ~27% in case-control or two-arm cohort studies, and ~80% in single-arm cohort studies. These findings are consistent with the results from previous reviews (Sayasneh *et al*, 2011; Pearce *et al*, 2012; Heidemann *et al*, 2014). Furthermore, these findings were similar in subgroup analyses to minimise bias, suggesting the epidemiologic evidence than endometriosis may be strongly associated with the increased risk of ovarian cancer. Second, early-stage disease,

Figure 3. (Continued)

Table 3. Subgroup analyses for evaluating clinicopathologic characteristics of endometriosis-associated ovarian cancer

				Heterogeneity		
Category	No. of studies with references	RR	95% CI	P	I ²	Model used
FIGO stage I–II disease						
Study design						
Case–control	2	1.983	1.683–2.336	0.973	0	Fixed effect
Cohort	4	1.920	1.020–3.616	<0.001	91.975	Random effects
Adjustment for potential confounding factors						
Age	5	1.973	1.297–3.003	<0.001	89.656	Random effects
Grade 1 disease						
Study design						
Case–control	14	1.354	1.169–1.568	0.743	0	Fixed effect
Quality of study (NOS)						
≥7	11	1.328	1.155–1.528	0.456	0	Fixed effect
<7	4	1.087	0.518–2.280	0.963	0	Fixed effect
Assessment of endometriosis						
Histology	3	1.801	0.898–3.610	0.063	63.872	Random effects
Self-report	12	1.303	1.121–1.515	0.945	0	Fixed effect
Adjustment for potential confounding factors						
Two factors ^a	13	1.330	1.147–1.543	0.858	0	Fixed effect
Eight factors ^b	12	1.303	1.121–1.515	0.945	0	Fixed effect
Nulliparity						
Assessment of endometriosis						
Histology	3	1.648	1.212–2.241	0.150	47.262	Fixed effect
Adjustment for potential confounding factors						
Age	3	1.319	1.237–1.407	0.308	15.038	Fixed effect
Optimal debulking surgery						
Study design						
Case–control	2	1.739	0.630–4.799	<0.001	97.838	Random effects
Cohort	3	1.147	0.973–1.352	0.239	30.192	Fixed effect
Adjustment for potential confounding factors						
Age	4	1.376	0.827–2.290	<0.001	94.729	Random effects

Abbreviations: CI = confidence interval; FIGO = International Federation of Gynecology and Obstetrics; NOS = Newcastle–Ottawa Scale; RR = risk ratio.

^aAdjusted for age and race.

^bAge, body mass index, breastfeeding, family history of ovarian cancer, history of tubal ligation, parity, race, and use of oral contraceptive.

low-grade disease and endometrioid and clear cell carcinomas were strongly associated with EAO and non-EAO. Recently, a dualistic model for ovarian carcinogenesis has been suggested. Type I ovarian tumours are clinically indolent and usually present with low-grade carcinoma, showing *KRAS*, *BRAF*, *ERBB2*, *PTEN*, *CTNNB1* and *PIK3-CA* mutations. These mutations exhibit the continuum of tumour progression between benign cystic neoplasms and the corresponding carcinomas such as endometrioid, clear cell and low-grade serous carcinomas, often through precursor lesions such as ES and borderline tumours (Cho and Shih, 2009). On the other hand, type II ovarian tumours are highly aggressive and almost always present in advanced-stage disease, showing *TP53* mutation (Bast *et al*, 2009). Our meta-analytic results show the epidemiologic evidence that EAO may have favourable characteristics of type I ovarian tumours. Furthermore,

we found that the risk of EAO increased in relatively young or nulliparous women, and this also suggests the epidemiologic evidence that the retrograde menstruation and activation of oncogenic pathways in eutopic endometrium may permit endometrial tissues to implant and invade on ovarian and peritoneal surfaces that leads to type I ovarian tumours (Bulun, 2009).

In particular, a specific histology such as endometrioid or clear cell carcinoma supports the hypothetical pathogenesis of malignant transformation of endometriosis. In the hypothesis, the carcinogenic process in an oestrogen-rich, progesterone-poor hormonal environment primarily gives rise to endometrioid carcinoma (Ness, 2003; Mandai *et al*, 2009). Moreover, a high-level of heme and free iron induces persistent oxidative stress that results in stress-resistant type such as clear cell carcinoma

Table 4. Subgroup analyses for evaluating histologic types of endometriosis-associated ovarian cancer

				Heterogeneity		
Category	No. of studies with references	RR	95% CI	P	I ²	Model used
Serous carcinoma						
Study design						
Case-control	15	0.774	0.654–0.915	<0.001	66.897	Random effects
Cohort	2	0.371	0.218–0.642	0.349	0	Fixed effect
Quality of study (NOS)						
≥7	13	0.729	0.591–0.900	<0.001	74.977	Random effects
<7	4	0.772	0.630–0.946	0.435	0	Fixed effect
Assessment of endometriosis						
Histology	3	0.408	0.064–2.585	<0.001	94.296	Random effects
Self-report	13	0.776	0.709–0.851	0.854	0	Fixed effect
Adjustment for potential confounding factors						
Two factors ^a	15	0.793	0.687–0.916	0.004	56.276	Random effects
Eight factors ^b	14	0.767	0.701–0.840	0.685	0	Fixed effect
Mucinous carcinoma						
Study design						
Case-control	15	0.777	0.559–1.080	0.698	0	Fixed effect
Cohort	2	1.475	0.377–5.768	0.227	31.613	Fixed effect
Quality of study (NOS)						
≥7	13	0.887	0.612–1.285	0.474	0	Fixed effect
<7	4	0.606	0.321–1.144	0.934	0	Fixed effect
Assessment of endometriosis						
Histology	3	0.565	0.106–3.001	0.091	58.373	Random effects
Self-report	13	0.753	0.530–1.069	0.900	0	Fixed effect
Adjustment for potential confounding factors						
Two factors ^a	15	0.852	0.614–1.181	0.759	0	Fixed effect
Eight factors ^b	14	0.795	0.565–1.120	0.826	0	Fixed effect
Endometrioid carcinoma						
Study design						
Case-control	15	1.684	1.479–1.917	0.611	0	Fixed effect
Cohort	2	3.886	1.457–10.360	0.067	70.206	Random effects
Quality of study (NOS)						
≥7	13	1.788	1.557–2.054	0.046	43.661	Fixed effect
<7	4	1.630	1.210–2.194	0.790	0	Fixed effect
Assessment of endometriosis						
Histology	3	2.837	1.417–5.677	0.043	68.249	Random effects
Self-report	13	1.595	1.380–1.843	0.692	0	Fixed effect
Adjustment for potential confounding factors						
Two factors ^a	15	1.634	1.422–1.878	0.695	0	Fixed effect
Eight factors ^b	14	1.629	1.414–1.875	0.629	0	Fixed effect
Clear cell carcinoma						
Study design						
Case-control	15	2.454	2.077–2.899	0.591	0	Fixed effect
Cohort	2	4.514	1.905–10.693	0.085	66.234	Random effects
Quality of study (NOS)						
≥7	13	2.518	2.111–3.003	0.147	29.680	Fixed effect
<7	4	3.012	2.100–4.321	0.500	0	Fixed effect
Assessment of endometriosis						
Histology	3	3.118	1.301–7.472	0.024	73.229	Random effects
Self-report	13	2.504	2.103–2.981	0.484	0	Fixed effect
Adjustment for potential confounding factors						
Two factors ^a	15	2.486	2.108–2.931	0.579	0	Fixed effect
Eight factors ^b	14	2.526	2.132–2.992	0.552	0	Fixed effect

Abbreviations: CI = confidence interval; FIGO = International Federation of Gynecology and Obstetrics; NOS = Newcastle–Ottawa Scale; RR = risk ratio.

^aAdjusted for age and race.^bAge, body mass index, breastfeeding, family history of ovarian cancer, history of tubal ligation, parity, race, and use of oral contraceptive.

(Mandai *et al*, 2009). Furthermore, genetic mutations in *hepatocyte nuclear factor-1 β* (*HNF-1 β*) and *ARID1A* are known to be related with the onset of endometrioid or clear cell carcinoma from endometriosis (Kato *et al*, 2006; Wiegand *et al*, 2010). Nevertheless, we found a relatively low incidence of serous carcinoma in EAO, and no impact of endometriosis on the risk of mucinous carcinoma.

On the other hand, the recent pooled analysis showed that endometriosis was not associated with the risk of mucinous carcinoma of the ovary (odd ratio (OR), 1.02; 95% CI, 0.69–1.50), whereas it increased the risk of low-grade serous carcinoma (OR, 2.11; 95% CI, 1.39–3.20) and did not affect the risk of high-grade serous carcinoma in the recent pooled analysis (OR, 1.13; 95% CI, 0.97–1.32) (Pearce *et al*, 2012). These conflicting results on the meta-analysis are because of a number of included studies, study design, quality of study and adjustment for potential confounding factors. When compared with the previous pooled analysis using 13 case–control studies, more studies (15 case–control and two cohort studies) for histology were included in this meta-analysis, and all results were obtained in both crude and subgroup analyses for minimising bias that made the results more persuasive. Furthermore, the result that endometriosis was associated with a lower risk of serous adenocarcinoma is reasonable in this meta-analysis when we considered that endometriosis was related with the increased risk of endometrioid and clear cell carcinomas, and mucinous carcinoma was not associated with endometriosis.

Third, endometriosis did not affect prognosis of ovarian cancer. Although there was no difference in progression-free survival between the two groups, EAO was associated with better overall survival than non-EAO in crude analyses. These findings explain why previous studies have suggested better prognosis of EAO with favourable characteristics including early-stage disease, low-grade disease and a specific histology up to now (Erzen *et al*, 2001). However, there were no differences in both progression-free survival and overall survival between the two groups in subgroup analyses based on histology, assessment of endometriosis, disease status and adjustment for potential confounding factors. These findings mean that endometriosis may not affect prognosis of ovarian cancer in spite of favourable characteristics of type I ovarian tumours, and previous studies have also demonstrated no benefit of survival in patients with EAO when controlled with FIGO stage (McMeekin *et al*, 1995; Komiya *et al*, 1999; Kumar *et al*, 2011). Moreover, the impact of endometriosis on probability of optimal debulking surgery, the most important prognostic factor in ovarian cancer, was not determined in the meta-analysis, suggesting no benefit of survival in patients with EAO indirectly.

In conclusion, endometriosis is strongly associated with the increased risk of ovarian cancer risk. Furthermore, favourable factors of EAO including early-stage disease, low-grade disease and a specific histology such as endometrioid or clear cell carcinoma belong to type I ovarian tumours showing less invasiveness and slow growth, which supports the epidemiologic evidence linking endometriosis to a precursor lesion of ovarian cancer. In spite of favourable characteristics of EAO, there was no difference in prognosis between EAO and non-EAO when adjusted with stage and a specific histology that suggests that endometriosis may not affect the progression after the onset of ovarian cancer.

These results from this meta-analysis suggest the possibility of no difference in the efficacy of primary standard treatment including cytoreductive surgery and adjuvant taxane- and platinum-based chemotherapy between EAO and non-EAO. Thus, prospective clinical trials are required to determine the surgical extent to remove endometriosis as well as tumour, and the optimal regimen and cycles of adjuvant chemotherapy based on clinicopathologic characteristics of EAO for improving its prognosis.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

HSK conceived and designed the study, selected and interpreted the data and drafted the manuscript; HHC selected the articles; THK retrieved the data; YSS designed the study and revised the manuscript. All authors approved the final version of the manuscript.

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