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 I² to select fixed-effect (I² ≤ 50%) or random effects models (I² > 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
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., 2008). However, ovarian cancer is known to develop in 0.3–1.6% of women with endometriosis (Mostoufizadeh and Scully, 1980; Seidman, 1996; Swierz, 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; Orezzoli 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; Orezzoli et al., 2008; Rossing et al., 2008; Kumar et al., 2011; Wang et al., 2013), whereas these

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**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 (Komiyama 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 EAOC 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 EAOC and non-EAOC 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

| Category | No. of studies with references | RR or SIR | 95% CI | P | I² | 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 |
| Historyology | 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 factorsa | 17 | 1.270 | 1.211–1.332 | 0.760 | 0 | Fixed effect |
| Eight factorsb | 14 | 1.254 | 1.192–1.319 | 0.961 | 0 | Fixed effect |
| **Single-arm cohort studies** | | | | | | |
| Assessment of endometriosis | | | | | | |
| Historyology | 4 | 1.463 | 1.233–1.749 | 0.559 | 0 | Fixed effect |
| Adjustment for potential confounding factors | | | | | | |
| Two factorsa | 4 | 1.507 | 1.255–1.810 | 0.023 | 68.416 | Random effects |
| Three factorsa | 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 clinicopathologic 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; Ziozias 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 including 444,255 patients were included in the meta-analysis (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; Orezzoli 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 two-arm cohort studies; numbers of observed and expected events; dichotomous data eligible in each study were shown as a risk ratio (RR) with its 95% confidence interval (CI) in 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 $I^2 > 50%$...
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 EAOC and non-EAOC patients in eight relevant studies with NOS score \( \geq 7 \) that included 47,047 patients, the characteristics of which are summarised in Supplementary Table 5. In most of the studies, patients with EAOC were relatively young in comparison with those with non-EAOC. In terms of survival, there was no difference in progression-free survival between EAOC and non-EAOC (HR, 1.023; 95% CI, 0.712–1.470; Figure 2A), whereas EAOC was associated with a better overall survival than non-EAOC 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 EAOC and non-EAOC 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 EAOC and non-EAOC in six cohort studies including 46,563 patients and 15 case-control studies including 8,417 patients. General characteristics are depicted in Supplementary Table 6. In crude analyses, FIGO stage I–II disease (RR, 1.359; 95% CI, 1.187–2.187; 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 |
|-----------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Category                                 | No. of studies | 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                                | 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

### Table A

| Model          | Study name     | Risk ratio | Lower limit | Upper limit | Risk ratio and 95% CI | Relative weight |
|----------------|----------------|------------|-------------|-------------|-----------------------|-----------------|
|                | McMeekin et al, 1995 | 1.859      | 1.229       | 2.811       | 15.66                 |                 |
|                | Komiyama et al, 1999 | 1.100      | 0.748       | 1.618       | 16.09                 |                 |
|                | Erzen et al, 2001   | 1.980      | 1.656       | 2.389       | 18.83                 |                 |
|                | Orezzoli et al, 2008| 1.573      | 1.038       | 2.384       | 15.63                 |                 |
|                | Kumar et al, 2011   | 1.996      | 1.330       | 2.993       | 15.79                 |                 |
|                | Wang et al, 2013    | 4.043      | 3.140       | 5.205       | 17.99                 |                 |
| Random Total (summary) | 1.959      | 1.367       | 2.807       |             |                       |                 |

Heterogeneity: $P<0.001; I^2=87.231%$

### Table B

| Model          | Study name     | Risk ratio | Lower limit | Upper limit | Risk ratio and 95% CI | Relative weight |
|----------------|----------------|------------|-------------|-------------|-----------------------|-----------------|
|                | McMeekin et al, 1995 | 1.091      | 0.733       | 1.624       | 11.98                 |                 |
|                | Ziogas et al, 2000  | 1.305      | 1.104       | 1.542       | 67.85                 |                 |
|                | Erzen et al, 2001   | 2.898      | 1.092       | 7.694       | 1.99                  |                 |
|                | Royar et al, 2001   | 0.911      | 0.182       | 4.553       | 0.73                  |                 |
|                | Glud et al, 2004    | 1.220      | 0.606       | 2.458       | 3.87                  |                 |
|                | Pike et al, 2004    | 1.218      | 0.488       | 3.039       | 2.27                  |                 |
|                | Terry et al, 2005   | 1.283      | 0.398       | 4.130       | 1.39                  |                 |
|                | Risch et al, 2006   | 2.783      | 0.556       | 13.938      | 0.73                  |                 |
|                | Merrit et al, 2008  | 1.079      | 0.393       | 2.961       | 1.86                  |                 |
|                | Moorman et al, 2008 | 0.839      | 0.307       | 2.288       | 1.88                  |                 |
|                | Rossing et al, 2008 | 3.176      | 1.025       | 9.840       | 1.48                  |                 |
|                | Cunningham et al, 2009 | 1.168    | 0.062       | 22.046      | 0.22                  |                 |
|                | Balogun et al, 2011 | 0.592      | 0.035       | 10.002      | 0.24                  |                 |
|                | Kumar et al, 2011   | 2.545      | 1.086       | 5.967       | 2.61                  |                 |
|                | Ness et al, 2011    | 1.502      | 0.348       | 6.485       | 0.89                  |                 |
| Fixed Total (summary) | 1.319      | 1.149       | 1.514       |             |                       |                 |

Heterogeneity: $P=0.734; I^2=0%$

### Table C

| Model          | Study name     | Risk ratio | Lower limit | Upper limit | Risk ratio and 95% CI | Relative weight |
|----------------|----------------|------------|-------------|-------------|-----------------------|-----------------|
|                | McMeekin et al, 1995 | 2.438      | 1.277       | 4.651       | 0.98                  |                 |
|                | Komiyama et al, 1999 | 2.200      | 1.135       | 4.266       | 0.94                  |                 |
|                | Orezzoli et al, 2008| 1.259      | 0.834       | 1.899       | 2.42                  |                 |
|                | Melin et al, 2011   | 1.314      | 1.231       | 1.403       | 95.66                 |                 |
| Fixed Total (summary) | 1.327      | 1.245       | 1.415       |             |                       |                 |

Heterogeneity: $P=0.073; I^2=57.002%$

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.
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 non-genetic 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 optimally debulking surgery.

| Model | Study name | Risk ratio | Lower limit | Upper limit | Risk ratio and 95% CI | Relative weight |
|-------|------------|------------|-------------|-------------|----------------------|----------------|
| McMeekin et al, 1995 | 1.527 | 1.049 | 2.223 | 18.65 |
| Komiya et al, 1999 | 1.120 | 0.813 | 1.544 | 19.41 |
| Erzen et al, 2001 | 2.925 | 2.324 | 3.682 | 20.49 |
| Orezzoli et al, 2008 | 1.049 | 0.839 | 1.311 | 20.57 |
| Kumar et al, 2011 | 1.038 | 0.859 | 1.256 | 20.89 |
| Total (summary) | 1.403 | 0.915 | 2.152 | 0.1 0.2 0.5 1 2 5 10 |

**Heterogeneity:** $P<0.001; I^2=93.014\%$

**Serous carcinoma**

| Model | Study name | Risk ratio | Lower limit | Upper limit | Risk ratio and 95% CI | Relative weight |
|-------|------------|------------|-------------|-------------|----------------------|----------------|
| Ziogas et al, 2000 | 0.715 | 0.517 | 0.988 | 7.47 |
| Erzen et al, 2001 | 0.132 | 0.051 | 0.343 | 2.47 |
| Royar et al, 2001 | 0.770 | 0.154 | 3.841 | 1.03 |
| Glud et al, 2004 | 0.855 | 0.426 | 1.717 | 8.42 |
| Pike et al, 2004 | 0.864 | 0.676 | 1.105 | 7.86 |
| Terry et al, 2005 | 0.707 | 0.528 | 0.947 | 6.22 |
| Risch et al, 2006 | 0.593 | 0.386 | 0.911 | 6.22 |
| Merrit et al, 2008 | 0.761 | 0.609 | 0.951 | 8.63 |
| Moorman et al, 2008 | 0.827 | 0.659 | 1.038 | 8.02 |
| Risch et al, 2006 | 0.938 | 0.710 | 1.239 | 8.63 |
| Cunningham et al, 2009 | 0.578 | 0.358 | 0.933 | 5.68 |
| Aris, 2010 | 0.438 | 0.232 | 0.827 | 4.26 |
| Lurie et al, 2010 | 0.781 | 0.509 | 1.197 | 4.56 |
| Balogun et al, 2011 | 0.620 | 0.341 | 1.129 | 7.12 |
| Kumar et al, 2011 | 1.832 | 1.287 | 2.607 | 7.35 |
| Ness et al, 2011 | 0.778 | 0.557 | 1.087 | 2.19 |
| Wang et al, 2013 | 0.246 | 0.088 | 0.689 | 2.19 |
| Total (summary) | 0.733 | 0.617 | 0.871 | 0.1 0.2 0.5 1 2 5 10 |

**Heterogeneity:** $P<0.001; I^2=68.474\%$

**Mucinous carcinoma**

| Model | Study name | Risk ratio | Lower limit | Upper limit | Risk ratio and 95% CI | Relative weight |
|-------|------------|------------|-------------|-------------|----------------------|----------------|
| Ziogas et al, 2000 | 0.840 | 0.301 | 2.348 | 9.72 |
| Erzen et al, 2001 | 0.160 | 0.022 | 1.156 | 2.62 |
| Royar et al, 2001 | 1.023 | 0.075 | 13.996 | 1.50 |
| Glud et al, 2004 | 0.858 | 0.039 | 8.781 | 1.48 |
| Pike et al, 2004 | 0.519 | 0.233 | 1.157 | 15.96 |
| Terry et al, 2005 | 0.206 | 0.029 | 1.465 | 2.66 |
| Risch et al, 2006 | 1.305 | 0.395 | 4.308 | 7.19 |
| Merrit et al, 2008 | 1.252 | 0.506 | 3.067 | 12.51 |
| Moorman et al, 2008 | 0.645 | 0.204 | 2.044 | 7.72 |
| Rossing et al, 2008 | 0.174 | 0.011 | 2.837 | 1.32 |
| Cunningham et al, 2009 | 0.764 | 0.102 | 5.710 | 2.54 |
| Aris, 2010 | 2.374 | 0.496 | 11.372 | 4.18 |
| Lurie et al, 2010 | 0.608 | 0.196 | 1.886 | 8.01 |
| Balogun et al, 2011 | 0.742 | 0.187 | 2.954 | 5.38 |
| Kumar et al, 2011 | 1.752 | 0.577 | 5.318 | 8.33 |
| Ness et al, 2011 | 1.085 | 0.340 | 3.461 | 7.63 |
| Wang et al, 2013 | 0.333 | 0.021 | 5.317 | 1.34 |
| Total (summary) | 0.805 | 0.584 | 1.109 | 0.1 0.2 0.5 1 2 5 10 |

**Heterogeneity:** $P=0.665; I^2=0\%$

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 of 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 EAOC and non-EAOC 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,

### G

**Endometrioid carcinoma**

| Model | Study name | Risk ratio | Lower limit | Upper limit | Risk ratio and 95% CI | Relative weight |
|-------|------------|------------|-------------|-------------|-----------------------|-----------------|
| Fixed | Total (summary) | 1.759 | 1.551 | 1.995 | | |

Heterogeneity: $P=0.123$; $I^2=29.370\%$

### H

**Clear cell carcinoma**

| Model | Study name | Risk ratio | Lower limit | Upper limit | Risk ratio and 95% CI | Relative weight |
|-------|------------|------------|-------------|-------------|-----------------------|-----------------|
| Fixed | Total (summary) | 2.606 | 2.225 | 3.053 | | |

Heterogeneity: $P=0.211$; $I^2=20.784\%$

Figure 3. (Continued)
low-grade disease and endometrioid and clear cell carcinomas were strongly associated with EAOC and non-EAOC. 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 \textit{KRAS}, \textit{BRAF}, \textit{ERBB2}, \textit{PTEN}, \textit{CTNNB1} and \textit{PIK3CA} 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 \textit{TP53} mutation (Bast et al., 2009).

Our meta-analytic results show the epidemiologic evidence that EAOC may have favourable characteristics of type I ovarian tumours. Furthermore, we found that the risk of EAOC 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.

| 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) |
| \( \geq 7 \) | 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* | 13 | 1.330 | 1.147–1.543 | 0.858 | 0 | Fixed effect |
| Eight factors** | 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 |
| 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.

*Adjusted for age and race.

**Age, body mass index, breastfeeding, family history of ovarian cancer, history of tubal ligation, parity, race, and use of oral contraceptive.
### Table 4. Subgroup analyses for evaluating histologic types of endometriosis-associated ovarian cancer

| Category               | No. of studies with references | RR     | 95% CI     | \( P \)  | \( \hat{I}^2 \) | Model used       |
|------------------------|--------------------------------|--------|------------|---------|------------|------------------|
| **Serous carcinoma**   |                                |        |            |         |            |                  |
| **Study design**       |                                |        |            |         |            |                  |
| Case–control           | 15 2                           | 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)** |                           |        |            |         |            |                  |
| \( \geq 7 \)           | 13 4                           | 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 13                          | 0.408  | 0.064–2.585| <0.001  | 94.296     | Random effects   |
| Self-report            | 3                             | 0.776  | 0.709–0.851| 0.185   | 0          | Fixed effect     |
| **Adjustment for potential confounding factors** |                   |        |            |         |            |                  |
| Two factors\(^a\)      | 15 14                         | 0.793  | 0.687–0.916| 0.004   | 56.276     | Random effects   |
| Eight factors\(^b\)   | 15 14                         | 0.767  | 0.701–0.840| 0.685   | 0          | Fixed effect     |
| **Mucinous carcinoma** |                                |        |            |         |            |                  |
| **Study design**       |                                |        |            |         |            |                  |
| Case–control           | 15 2                           | 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)** |                           |        |            |         |            |                  |
| \( \geq 7 \)           | 13 4                           | 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 13                          | 0.565  | 0.106–3.001| 0.091   | 58.373     | Random effects   |
| Self-report            | 3                             | 0.753  | 0.530–1.069| 0.900   | 0          | Fixed effect     |
| **Adjustment for potential confounding factors** |                   |        |            |         |            |                  |
| Two factors\(^a\)      | 15 14                         | 0.852  | 0.614–1.181| 0.759   | 0          | Fixed effect     |
| Eight factors\(^b\)   | 15 14                         | 0.795  | 0.565–1.120| 0.826   | 0          | Fixed effect     |
| **Endometrioid carcinoma** |                              |        |            |         |            |                  |
| **Study design**       |                                |        |            |         |            |                  |
| Case–control           | 15 2                           | 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)** |                           |        |            |         |            |                  |
| \( \geq 7 \)           | 13 4                           | 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 13                          | 2.837  | 1.417–5.677| 0.043   | 68.249     | Random effects   |
| Self-report            | 3                             | 1.595  | 1.380–1.843| 0.692   | 0          | Fixed effect     |
| **Adjustment for potential confounding factors** |                   |        |            |         |            |                  |
| Two factors\(^a\)      | 15 14                         | 1.634  | 1.422–1.878| 0.695   | 0          | Fixed effect     |
| Eight factors\(^b\)   | 15 14                         | 1.629  | 1.414–1.875| 0.629   | 0          | Fixed effect     |
| **Clear cell carcinoma** |                              |        |            |         |            |                  |
| **Study design**       |                                |        |            |         |            |                  |
| Case–control           | 15 2                           | 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)** |                           |        |            |         |            |                  |
| \( \geq 7 \)           | 13 4                           | 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 13                          | 3.118  | 1.301–7.472| 0.024   | 73.229     | Random effects   |
| Self-report            | 3                             | 2.504  | 2.103–2.981| 0.484   | 0          | Fixed effect     |
| **Adjustment for potential confounding factors** |                   |        |            |         |            |                  |
| Two factors\(^a\)      | 15 14                         | 2.486  | 2.108–2.931| 0.579   | 0          | Fixed effect     |
| Eight factors\(^b\)   | 15 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.

\(^a\)Adjusted for age and race.

\(^b\)Age, body mass index, breastfeeding, family history of ovarian cancer, history of tubal ligation, parity, race, and use of oral contraceptive.
surgical extent to remove endometriosis as well as tumour, and the including cytoreductive surgery and adjuvant taxane- and no difference in the efficacy of primary standard treatment adjusted with stage and a specific histology that suggests that difference in prognosis between EAOC and non-EAOC when controlled with FIGO stage (McMeekin et al, 2009). 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 EAOC indirectly.

Third, endometriosis did not affect prognosis of ovarian cancer. Although there was no difference in progression-free survival between the two groups, EAOC was associated with better overall survival than non-EAOC in crude analyses. These findings explain why previous studies have suggested better prognosis of EAOC 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 EAOC when controlled with FIGO stage (McMeekin et al, 1995; Komiyama 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 EAOC indirectly.

In conclusion, endometriosis is strongly associated with the increased risk of ovarian cancer risk. Furthermore, favourable factors of EAOC 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 EAOC, there was no difference in prognosis between EAOC and non-EAOC 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 EAOC and non-EAOC. 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 EAOC 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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