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REVIEW

Impact of endometriosis on risk of ovarian, endometrial and cervical cancers: a meta-analysis

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Abstract

Purpose The risks of gynecologic cancer have not been well established in women with endometriosis. The objective of the present study was to investigate the influence of endometriosis on the risk for three gynecologic cancer (ovarian cancer, endometrial cancer and cervical cancer).

Methods We gathered updated evidence about the risk relationship between endometriosis and gynecologic cancers by conducting a comprehensive search of several medical literature electronic databases, including PubMed, Embase and the Cochrane Library. The design and quality of all studies were evaluated using the Newcastle–Ottawa Scale (NOS), and a random-effects model was used to calculate pooled risk ratio (RR).

Results Of the 8538 articles our search produced, we selected 25 qualified studies, including 16 cohort studies and 9 case–control studies. Patients with endometriosis had both an increased risk of ovarian cancer [RR 1.964; 95% CI (1.685, 2.290)]. The risk of endometrial cancer (EC) is not necessarily higher in patients with endometriosis [RR 1.176, 95% CI (0.878, 1.575)]. Endometriosis was not associated with an increased risk for cervical cancer (CC) [RR 0.670, 95% CI (0.537, 0.838)].

Conclusions Patients with endometriosis need to be closely observed and rechecked regularly to prevent malignant changes.

Keywords Endometriosis · Ovarian cancer · Endometrial cancer · Cervical cancer · Gynecological cancer · Risk

Introduction

Endometriosis is defined as the presence of endometrial-like tissue e.g., glands and stroma) or endometrium outside of the uterine cavity. It is a benign gynecological disease; however, it shows some characteristics similar to malignancy, such as tissue invasion, angiogenesis and the development of local and distant foci [1]. However, endometriosis is rarely fatal as it does not have the consequences of catabolism [1]. Therefore, according to the relevant classification criteria of the World Health Organization, endometriosis is classified as a tumor-like lesion at present [2].

A case of suspected malignant change in endometriosis was first recorded by Sampson in 1925 [3]. From then on, the association between endometriosis and gynecological cancers have been concentrated in some studies. A growing number of recent studies have supported the notion that endometriosis represents the initial stage of tumor progression. Atypical endometriosis is likely to represent a transitional form from benign disease to tumor.

Jia li and Ruijuan Liu contributed equally to this work and should be considered co-first authors.

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The association between endometriosis and gynecologic cancer, particularly ovarian cancer OC) and endometrial cancer EC), is especially compelling because of their shared common risk factors, including obesity, type 2 diabetes, hyperestrogenism, and reproductive characteristics [4]. Endometriosis itself is a risk factor for ovarian cancer [5, 6]. Most epidemiological studies have shown an increased risk of ovarian cancer in patients with endometriosis [7–9], but this association does not always exist [10]. A small number of studies have evaluated whether endometriosis is associated with the risk of endometrial cancer [11–14]. The results of these studies are inconclusive [8, 15]. To address these interesting and controversial issues, we conducted a meta-analysis with a large number of relevant studies published to date.

Materials and methods

Search strategy

The content of this meta-analysis strictly follows the PRISMA checklist for reporting. To conduct this meta-analysis, we comprehensively searched for the published relevant observational studies from the medical literature databases of PubMed, Embase and the Cochrane Library. The search terms were the following key words combined with their corresponding MeSH terms: (ovarian neoplasm and endometriosis) or (ovarian carcinoma and endometriosis) or (ovarian cancer and endometriosis) or (endometrial neoplasm and endometriosis) or (endometrial carcinoma and endometriosis) or (endometrial cancer and endometriosis) or (cervical neoplasms, uterine and endometriosis) or (cervix cancer and endometriosis). In addition, the references cited in included articles were manually searched to determine any additional studies that were not indexed by the database. For more information on our search criteria, please refer to the Annex.

Selection criteria and exclusion criteria

The relevant published manuscripts would be included if they met the following inclusion criteria: (1) studies that used a non-randomized controlled study (e.g., case–control, case–cohort), and investigated the risk relationship between endometriosis and OC, EC or CC; (2) usable risk estimates, such as odds ratio (OR), risk ratio (RR), hazard ratio (HR), standard incidence ratio (SIR) with 95% confidence intervals (CIs) were presented in the publication, or necessary data were given for calculation; (3) if several studies were conducted in the same population, we would select the report with the most applicable estimates or the most recent report. The exclusion criteria were as follows: (1) the study reported OC, EC or CC mortality or the survival relationship between women with endometriosis and OC, EC or CC; (2) reviews, case reports, editorials or letters to the editor; (3) studies did not meet the selection criteria.

Data abstraction

Two independent reviewers (Li and Liu) extracted data from each study according to the predetermined selection and exclusion criteria. When any discrepancies appeared, the two reviewers resolved disagreement by consulting with the third reviewer (Tang) and performed a joint reevaluation of the study. For each study, we independently extracted the first author's name, year of publication, study geographic region, study design, number of case and control, and categories of exposure with corresponding risk estimates as the basic content. If a study lacked relevant data, we were able to obtain the formation from pooled analyzes or systematic reviews.

Quality assessment

We used the Newcastle–Ottawa Scale NOS) to evaluate the quality of included studies cohort and case–control studies) [16]. The NOS composed of three parameters of quality: the selection, comparability and exposure or outcome of individual observational study. The NOS assigned up to four selection points at most—the comparability of the two points and the exposure or outcome of the three points. Two reviewers (Li and Liu) independently evaluated the quality, and any disagreements were solved by consulting with the third reviewer and re-evaluating the study.

Statistical analysis

Since all included studies were case–control studies or cohort studies, we interpreted all risk estimates, such as RR, OR, HR and SIR. We used all available ORs, RRs, HRs, and SIRs, or we recalculated the estimated value of the effect from available data [17]. As the absolute risk of ovarian cancer and endometrial cancer is low, the four combined measurement methods are expected to result in similar relative risk RR) estimates. Therefore, we put all the RR estimates together to ensure comprehensiveness of the analysis and to maximize the statistical effectiveness [18, 19]. The degree of heterogeneity in eligible studies was evaluated using the Q test. A value of $p < 0.10$ was considered statistically significant heterogeneity, and data were interpreted using the random effects model. For I^2, the values of 0%, 25%, 50%, and 75% respectively corresponds to the no, low, moderate, and high heterogeneity [20]. If $p > 0.10$, the fixed effect model was chosen. When significant heterogeneity existed across studies, we carried out a sub-analysis to confirm the source of heterogeneity and sensitivity analysis to evaluate

the robustness of the results. We used funnel plot to assess publication bias and quantified by the Begg's and Egger's test; $p < 0.05$ indicated statistical significance. We used STATA software to conduct all statistical analyzes.

Results

Literature search

A flow diagram summarizes the search process we used to identify relevant studies in Fig. 1. Of the 12,039 articles initially identified from the three databases, 3501 were identified as duplicates. The remaining 8538 articles were assessed by reviewing titles and abstracts. A total of 87 full texts were further assessed; 62 were excluded for various reasons, such as abstract form, form of summary, failure to include the usable data, and reporting results using the same study populations. Finally, 25 articles met the inclusion criteria and exclusion criteria, including 15 cohort studies [6, 11, 21–26, 29–32, 35, 38–40] and 10 case–control studies [27–29, 33, 34, 36, 37, 41, 42].

Study characteristics

The characteristics of the 25 included articles are shown in Table 1. All 25 articles were published between 1997 and 2017, and the study design types were as follows: cohort studies [$n = 15$ (7, 12, 22–27, 30–33, 36, 39, 40–41)], case–control studies [$n = 10$ (14, 28–29, 34–35, 37–38, 42–43)]. Studies were conducted in Taiwan [$n = 4$ (22, 24–26)], USA [$n = 8$ (7, 29, 34–36, 38–39, 42)], Australia [$n = 3$ (14, 23, 43)], Sweden [$n = 3$ (32, 34, 41)], and Denmark [$n = 2$ 12, 37)]. The Netherlands, Japan, Canada, and Spain each had one study [26, 40, 30, 29]. One study [10] encompassed the joint participation of multiple countries. Six studies [11, 21, 23, 29, 39, 40] explored the effects of age on OC, EC and CC in patients with endometriosis. With regards to the type of gynecologic cancer, 23 studies provided risk estimates for endometriosis and OC [6, 13, 21–24, 26–42], nine studies for endometriosis and EC [11, 22, 25, 13, 28, 31, 32, 35, 39], three studies for endometriosis and CC [31, 32, 39], five studies for endometriosis and endometrioid ovarian cancer [11, 21, 27, 29, 42], six studies for endometriosis and clear-cell type OC [11, 21, 27–29, 36] and one study for endometriosis and epithelioid ovarian cancer [24].

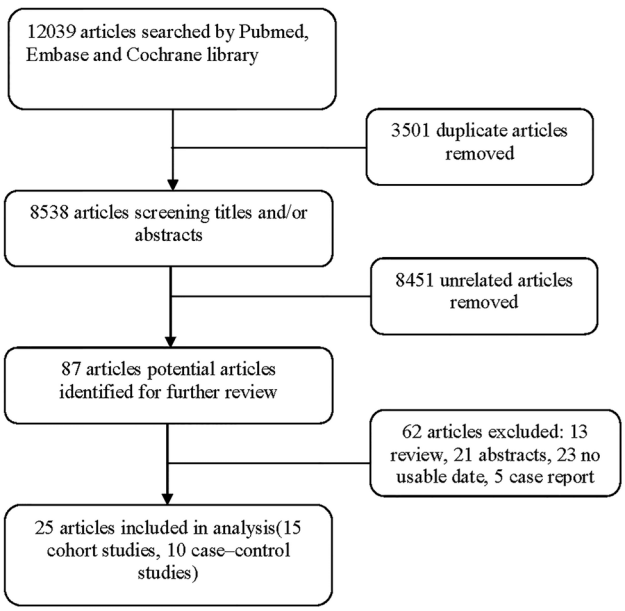

Fig. 1 Flow chart for selection of eligible studies

Risk analysis

We analyzed the relationship between endometriosis and three gynecological tumors (OC, EC, CC) with high incidence. Our overall analysis based on cancer type of the 37 studies described in the 25 selected articles showed that the weight of ovarian cancer is the highest (66.16%), the endometrial cancer is 24.67% and the weight of cervical cancer is the lowest (9.17%) (Fig. 2). The apparent heterogeneity was observed in the study results ($I^2 = 82.2\%$, $p = 0.00$) and thus, we choose the random effects model. We performed separate analyzes for these three tumors.

Ovarian cancer

Twenty-three articles [6, 11, 13, 21–24, 26–42], including a total of 25 studies, evaluated the risk relationship between endometriosis and ovarian cancer. In these 25 studies, endometriosis was associated with a significant increase [RR 1.964; 95% CI (1.685, 2.290)] in the incidence of ovarian cancer, although there was evidence of heterogeneity within the group ($Q = 99.847$, $p = 0.000$; $I^2 = 76.0\%$) (Fig. 3). We conducted a subgroup analysis of study types to clarify the reasons of heterogeneity. The results of the cohort studies ($p = 0.000$, $I^2 = 83.5\%$) and case–control studies ($p = 0.093$, $I^2 = 39.8\%$) suggest that different study types may be one of the sources of heterogeneity (Fig. 4). Publication bias was assessed by Begg's test and Egger's test. The p values for Begg's test and Egger's test were $p = 0.00$ and $p = 0.00$, respectively, suggesting that there was publication bias (supplement Fig. 1). To determine whether the conclusion of the study is robust, the sensitivity analysis was performed using the trim and fill method. The changes in the RR and the 95% CI before the trim and fill (RR 0.675, 95% CI 0.522,

Table 1 Characteristics of the 25 included studies

Author	Publication year	Location	Study population	Study type	OR/RR/HR/SIR (95% CI) of OC/EC/CC	Age factor (OC/EC)
Kuan-Chin	2014	Taiwan	168,927	Retrospective cohort study	OC 4.48 (95% CI 2.84-7.06) Endometrioid OC 3.70 (95% CI 1.62–8.46) Clear cell OC 7.36 (95% CI 1.91–28.33)	OC (age < 40): 1.66 (95% CI 0.36–7.61) OC (age > 40): 1.70 (95% CI 0.38–7.59) OC (age > 50): 4.97 (95% CI 1.03–4.09)
Louise M.	2013	Western Australia	21,646	Cohort study	OC 2.23 (95% CI 0.97–5.12) EC 4.05 (95% CI 1.20–13.66)	EC (age 31–40): 1.7 (95% CI 1.1–2.6) EC (age 41–50): 2.9 (95% CI 1.9–4.3) EC (age > 50): 4.2 (95% CI 2.4–7.6)
Victor C.	2015	Taiwan	36,274	Retrospective cohort study	OC 4.56 (95% CI 1.72–12.11)	
Wen-Hsun Chang	2014	Taiwan	22,611	Cohort study	Epithelioid OC 3.28 (95% CI 1.37–7.85)	
Hann-Chin	2015	Taiwan	139,392	Cohort study	EC 2.91 (95% CI 1.54–5.48)	
Buis	2013	Netherlands	8904	Cohort study	OC 11.6 (95% CI 2.7–50.2)	
Ingrid J.	2011	Australian	2938	Case–control study	EC 1.04 (95% CI 0.69–1.56)	
Celeste Leigh Pearce	2012	USA	21,137	Case–control study	OC 1.46 (95% CI 1.31–1.63) Endometrioid OC 2.04 (95% CI 1.67–2.48) Clear cell OC 3.73 (95% CI 3.04–4.58)	
Elizabeth M.	2017	USA	199,134	Case–control study	OC 1.81 (95% CI 1.26–2.58) Clear cell OC 1.78 (95% CI 0.84–3.78) EC 0.74 (95% CI 0.39–1.42)	
Pedro Acién	2015	Spain	239	Cohort study	Endometrioid OC 7.58 (95% CI 2.1–24.4) Clear cell OC 10.5 (95% CI 1.93–57.02)	OC (age > 50): 1.49 (95% CI 0.41–2.46)
Aziz Aris*	2010	Canada	2854	Cohort study	OC 1.6 (95% CI 1.12–2.09)	
Louise A	1997	Sweden	20,686	Cohort study	OC 1.9 (95% CI 1.3–2.8) EC 1.09 (95% CI 0.6–1.90) CC 0.7 (95% CI 0.4–1.3)	

Table 1 (continued)

Author	Publication year	Location	Study population	Study type	OR/RR/HR/SIR (95% CI) of OC/EC/CC	Age factor (OC/EC)
Julie Brøchner Mogensen	2016	Denmark	45,790	Cohort study	OC 1.34 (95% CI 1.16–1.55) Endometrioid OC 1.64 (95% CI 1.09–2.37) Clear cell OC 3.64 (95% CI 2.36–5.38) EC 1.43 (95% CI 1.13–1.79)	OC (age > 50): 2.27 (95% CI 1.61–3.10)
A. Melin1	2007	Sweden	63,630	Cohort study	OC 1.37 (95% CI 1.14–1.62) EC 1.14 (95% CI 0.93–1.39) CC 0.71 (95% CI 0.53–0.94)	
Modugno	2004	USA	5051	Case–control study	OC 1.32 (95% CI 1.06–1.65)	
Ness	2000	USA	2323	Case–control study	OC 1.7 (95% CI 1.2–2.4)	
Olsen	2002	USA	37,434	Cohort study	OC 0.78 (95% CI 0.25–2.44) EC 1.20 (95% CI 0.57–2.53)	
Louise A.	2005	Denmark	99,812	Case–control study	OC 1.69 (95% CI 1.27–2.25)	
Mary Anne	2009	USA	2125	Case–control study	OC 2.8 (95% CI 1.7–4.7)	
Louise A.	2005	USA	12,193	Cohort study	OC 1.25 (95% CI 0.6–2.6)	
Ness	2002	USA	12,912	Case–control study	OC 1.73 (95% CI 1.10–2.71)	
Christer Borgfeldt	2004	Sweden	NR	Cohort study	OC 1.34 (95% CI 1.03–1.75) EC 0.58 (95% CI 0.42–0.81) CC 0.57 (95% CI 0.37–0.90)	OC(age > 50): 0.98 (95% CI 0.42–2.31)
Kobayashi	2007	Japan	6398	Cohort study	OC 8.95 (95% CI 4.12–15.3)	OC (age 30–39): 4.85 (95% CI 2.09–7.74) OC (age 40–49): 8.03 (95% CI 4.78–11.9) OC (age > 50): 13.2 (95% CI 6.90-20.9)
Anna H. Wu	2009	USA	23,144	Case–control study	OC 1.66 (95% CI 1.01–2.75)	
Christina M.	2008	Australia	1598	Case–control study	Endometrioid OC 2.2 (95% CI 1.2–3.9) Clear cell OC 3.0 (95% CI 1.5–5.9)	

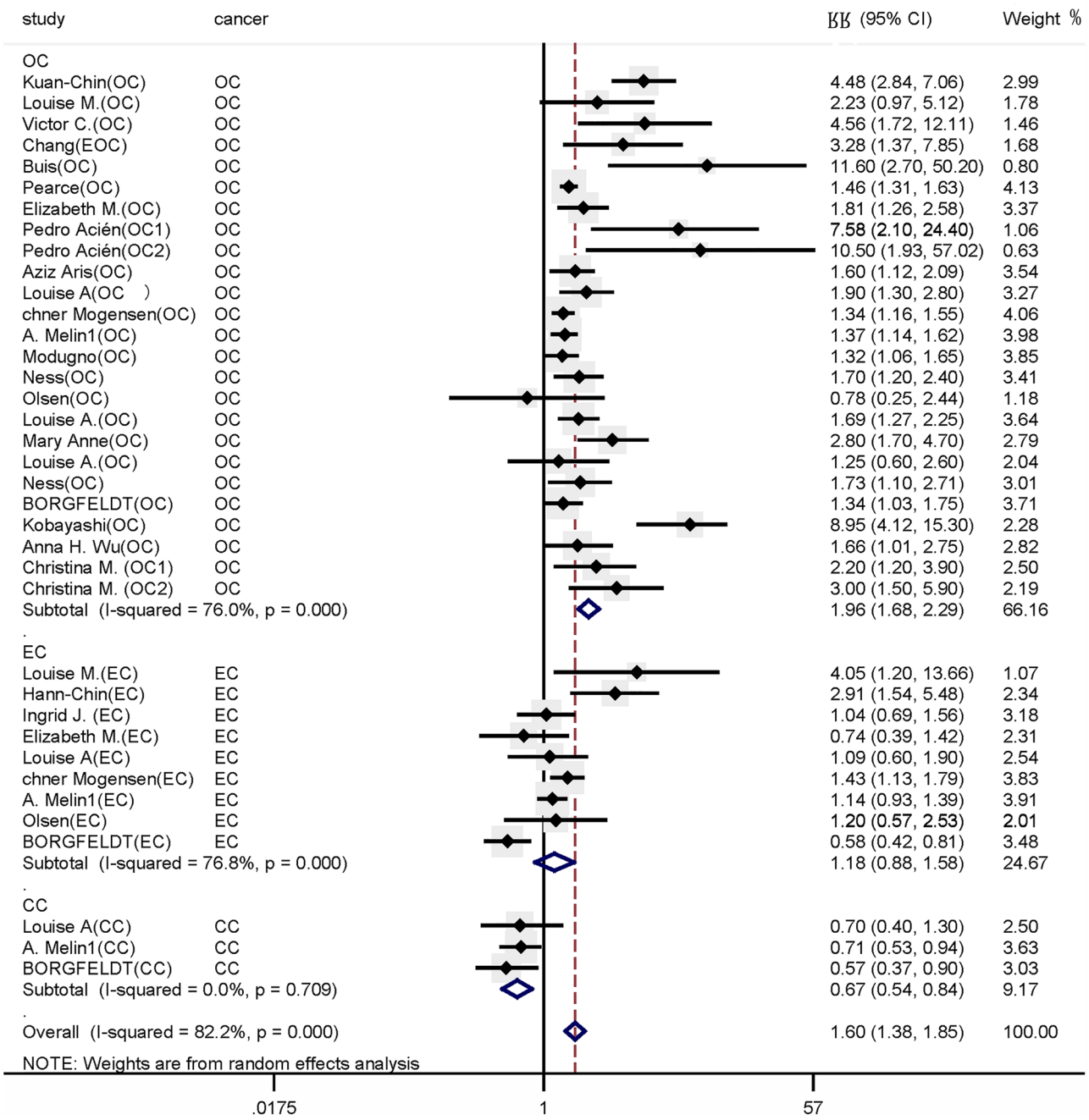

Fig. 2 Forest plot of the association between endometriosis and three gynecological tumors (OC, EC, CC): a subgroup analysis based on cancer type

0.828) and after [RR 1.502, 95% CI (1.263, 1.786)] are large, which means that the robustness of this analysis is low (supplement Fig. 2).

We also analyzed the subtype of ovarian cancer. The results showed that endometriosis increased the risk of endometrioid OC [RR 2.10, 95% CI (1.74, 2.53)] (supplement Fig. 3) and clear-cell type OC [RR 3.39, 95% CI (2.85, 4.02)] (supplement Fig. 4). There was lower heterogeneity observed in the study results; the Q values and I^2 were ($Q = 7.65$, $p = 0.176$; $I^2 = 34.7\%$) and ($Q = 7.28$, $p = 0.296$; $I^2 = 17.5\%$), respectively.

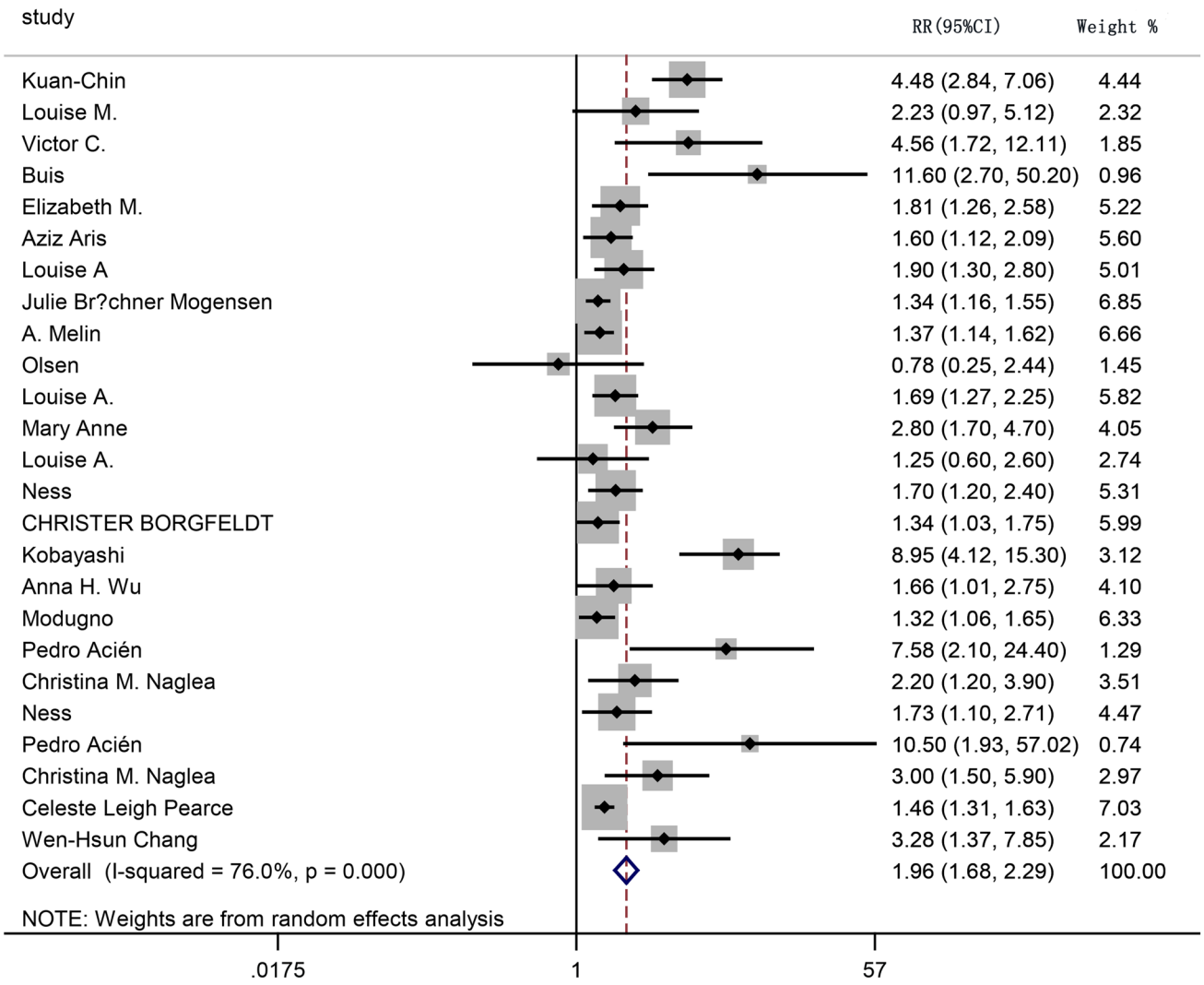

Fig. 3 Forest plot of the risk relationship between endometriosis and OC

Endometrial cancer

Nine articles [11, 13, 22, 25, 28, 31, 32], including a total of 9 studies, evaluated the association between endometriosis and endometrial cancer in incidence of risk. The results [RR 1.176, 95% CI (0.878, 1.575)] indicate that the risk of EC is not necessarily increased in patients with endometriosis (Fig. 5). Because of the heterogeneity ($Q = 34.491$, $p = 0.000$), we choose the random effects model to evaluate these data. U sing the correction and filling method for sensitivity analysis, the result showed a significant change in the RR and the 95% CI before pruning and filling [RR 0.162, 95% CI (− 0.130, 0.454)] and after [(RR 1.114, 95% CI (0.828, 1.499)], which indicates a lower robustness of the analysis (supplement Fig. 5). Using Begg's test and Egger's test to examine the publication bias, the p values were $p = 0.602$ and $p = 0.689$, respectively, indicating no apparent publication bias (supplement Fig. 6).

Cervical cancer

Three articles [31, 32, 39], including a total of 3 studies, evaluated the association between endometriosis and cervical cancer risk. Endometriosis was not associated with an increased risk for cervical cancer (CC) [RR 0.670, 95% CI (0.537, 0.838)]

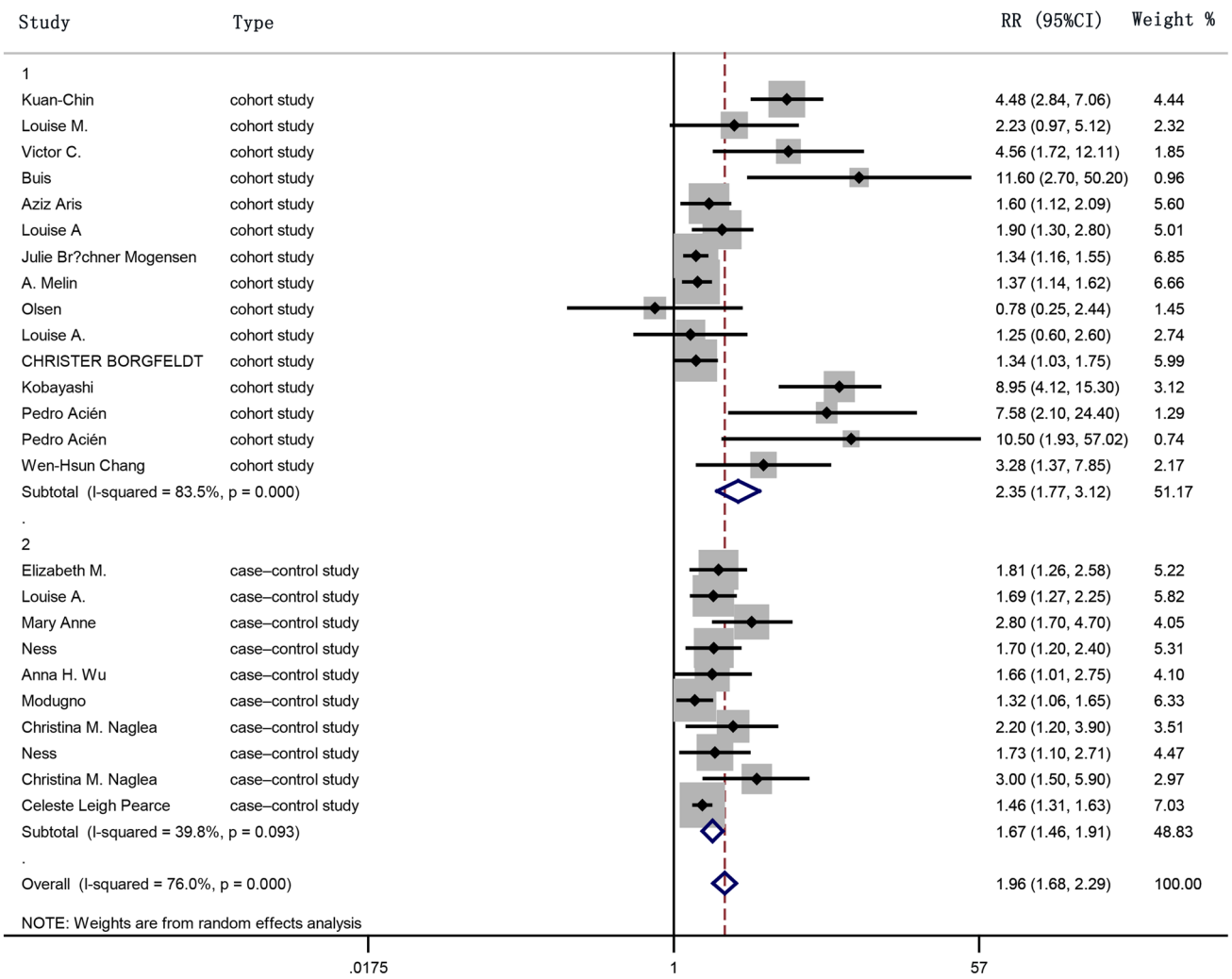

Fig. 4 A subgroup analysis of the risk relationship between endometriosis and OC based on the type of study design

(Fig. 5). No heterogeneity was observed in the study results ($Q=0.69$, $p=0.709$; $I^2=0.0\%$).

Discussion

Previous studies have analyzed only one of the risk relationships between endometriosis and ovarian cancer or endometrial cancer, while the risk relationship between endometriosis and three gynecologic oncology (OC, EC, CC) is still unclear. This is the first meta-analysis to our knowledge that reports an association between endometriosis and three gynecologic cancer risk. Our meta-analysis showed that endometriosis had different effects on various types of tumors. Specifically, endometriosis was associated with an increased risk of OC but was not necessarily associated with an increased risk of EC and was not associated with an increased risk for CC.

According to epidemiological and biological studies, endometriosis increased the risk of various malignancies. [43–46]. Endometriosis may cause cancer through a multistep phenomenon in which typical endometriosis becomes severe atypia, with or without hyperplasia, and then becomes cancer. A growing number of evidence suggested that endometriosis is associated with specific cancer types, but it is still difficult to draw definitive conclusions [15]. Our study conducted a summary analysis of various types of gynecological tumors to reach a more definitive conclusion.

The ovary is the major target organ for the malignant transformation of endometriosis, although the extragonadal may also be one of its origins [47]. Endometriosis increased susceptibility to developing some subtypes of epithelial ovarian cancer and exhibits some molecular similarities with cancer. This finding shows that endometriosis played a role in the process of tumorigenesis [48]. The results of genetic, biological and immunological studies

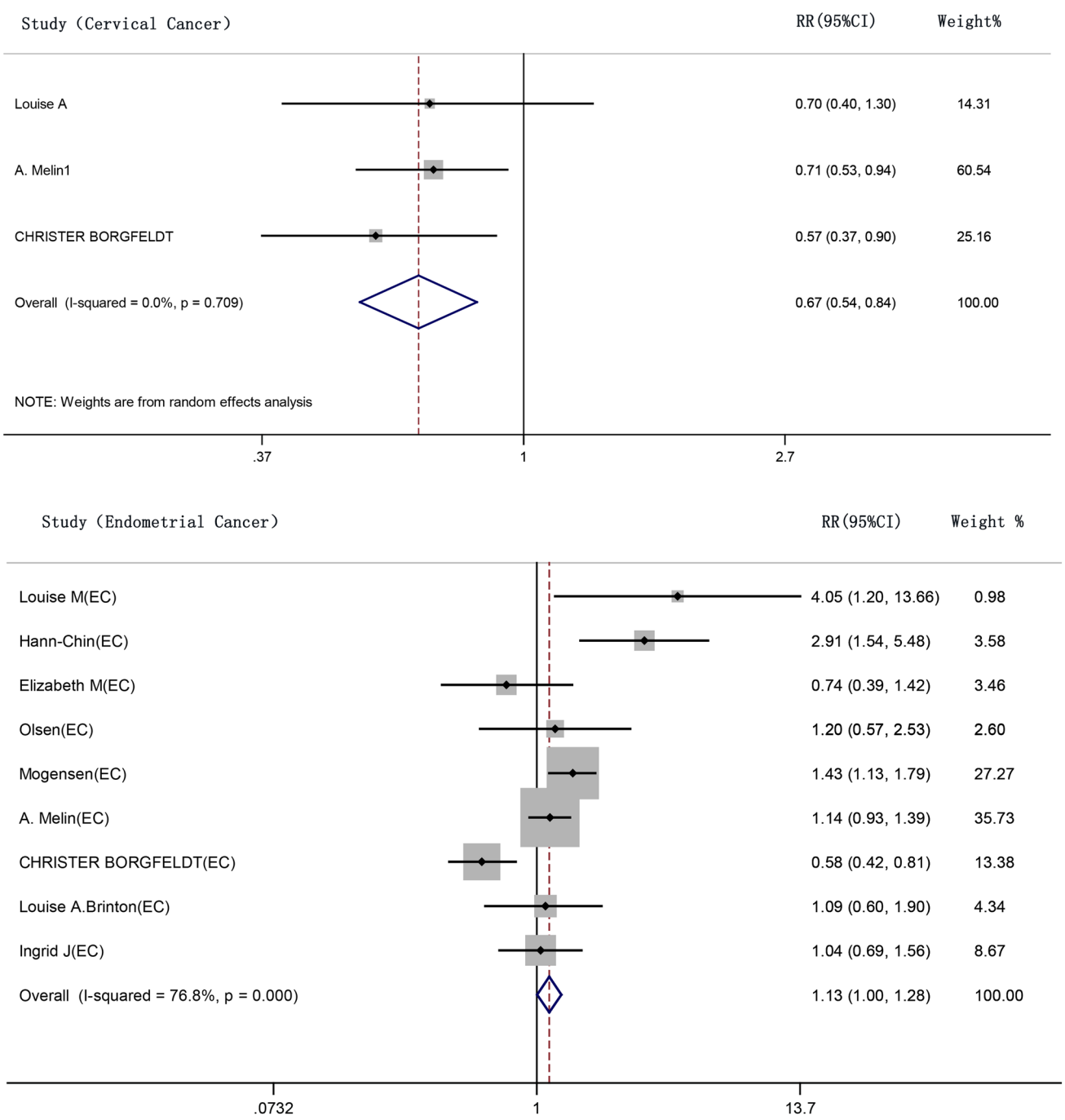

Fig. 5 Forest plot of the risk relationship between endometriosis and EC and CC

have shown that different types of genomic instability and mutations occur in endometriosis and ovarian cancer [49, 50]. Overexpression of p53, loss of oncogenic K-ras Pten, the defect of heterozygosity, and null allele of glutathione *S*-transferase M1 GSTM1) may participate in or promote the malignant transformation of endometriosis to ovarian cancer [51–54]. On the other hand, angiogenesis is considered to play an important role in the occurrence and development of endometriosis and malignancy [55]. Hayrabedyan et al. showed that the interleukins-1 IL-1), fibroblast growth factor FGF-1), and S100A13, as well as the common ovarian carcinoma marker were expressed in most of the studied cases, indicating a possible common pathological mechanism between endometriosis and ovarian cancer [56]. In addition, Chou et al. suggested that endometriosis malignant transformation to endometrioid ovarian cancer may cause COX-2

overexpression, and it may also result from the interaction between the two cell components [57].

The relationship between endometriosis and endometrial cancer may be interesting, considering that the eutopic endometrium, rather than endometriosis itself, may be the origin of eutopic and ectopic adenocarcinomas [15]. There is a putative association between endometriosis and endometrial cancer, as they have common etiological mechanisms including chronic inflammation and estrogen stimulation [25]. Similar to uterine or breast cancer, endometriosis is manifested as an estrogen-dependent disease; by enhancing the expression of aromatase cytochrome P450 and attenuating the expression of defective 17A-hydroxysteroid dehydrogenase type 2, local production of estrogen ER) is increased [58]. The expression of cyclooxygenase 2 COX-2) is elevated in patients with endometriosis and endometrial cancer and it is a rate-limiting enzyme in the biosynthesis of prostaglandin E2 [59]. Prostaglandin E2 can promote the initial carcinogenesis process, increases cell proliferation and neovascularization to further consolidate tumor progression while reducing in situ immune performance [60]. COX 2, ER and aromatase may have synergistic effects as their interconnections are very close; therefore, endometriosis is associated with endometrial cancer through chronic inflammation.

Although the above discussion convinced us that there is a risk relationship between endometriosis and three gynecologic tumors, our study also has some limitations. There are 26 eligible manuscripts for inclusion in our meta-analysis, which referred to four different effect size estimates (OR, RR, HR, SIR). Different effect sizes represent different meanings, and the absolute risk of ovarian cancer and endometrial cancer is low; thus, we combined the four types into relative risk (RR) estimates. However, SIR corresponds to RR estimates only for age and calendar time adjustments, usually leading to overestimation of cancer risk. The articles included were nonrandomized studies, most of which were retrospective studies. Therefore, the risk of recall bias is inevitable, and the lack of random allocation of the interventions may result in overestimation of RR. We observed a significant moderate–severe heterogeneity in major analyzes (ovarian cancer and endometrial carcinoma), which may be associated with the combination of four effect sizes. This heterogeneity is not surprising, given the variations in methods of study design, study population, study region, effect size, and adjustments across studies. Sensitivity analysis using the trim and fill method indicated that ovarian and endometrial cancer were slightly more robust. The less robustness of the analysis may decrease the credibility of our results, to a certain extent. In addition, in our research and analysis, ovarian cancer has a dominant position in the number and weight of research, which might lead to bias to some extent. These are a few of the limitations of the present meta-analysis.

Our study emphasized the risk relationship between endometriosis and gynecologic tumors (OC, EC, CC) and explored the pathogenesis from different perspectives to determine the risk relationship between them. Subgroup analyzes were conducted based on the type of study design, and the risk relationship between different subtypes and endometriosis were analyzed to refine the study contents. The research results are instructive in improving the treatment of patients with endometriosis.

Conclusion

Patients with endometriosis should be closely observed and regular tumor-related screening to prevent malignant transformation. However, as noted in the previous discussion, there is insufficient evidence to support the theory of endometriotic lesions as a precancerous lesion. If endometriosis is considered a precancerous lesion, the current treatment management needs to be modified.

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Author contributions Jia Li: select topic, literature search, data extraction and analysis, write the original article. Ruijuan Liu: select topic, literature search, data extraction and analysis, write of the review and editing. Shifeng Tang: data extraction, methodology. Fubin Feng: methodology. Cun Liu: the use of software, statistical analysis. Lu Wang: the use of software, statistical analysis. Wenge Zhao: validate the results, write the original article. Tingting Zhang: write, review, and edit the original article. Yan Yao: write the original article. Xue Wang: literature search. Changgang Sun: select topic, review original article.

Compliance with ethical standards

Conflict of interest The authors declare to have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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