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Endometriosis-associated Ovarian Cancer, from Risk Factors to Survival Rate: A Systematic Review and Meta-Analysis

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Abstract

Background: Endometriosis experts recommend monitoring patients until menopause before considering surgery, with concerns about lesion malignancy. This meta-analysis aims to assess the prevalence and prognosis of endometriosis-associated ovarian cancer (EAOC) in various types of epithelial ovarian cancer (EOC), and compare risk factors with the non-EAOC group to improve disease management.

Method: In this review, PubMed, Science Direct, Scopus, Google Scholar, and Cochrane databases were searched for "endometriosis" and "ovarian cancer risk factor" from 2010 to 2023. Papers not reporting cancer prevalence or without a specified sample size were excluded. The study used statistical Cochran's Q and I2 index tests to evaluate heterogeneity and estimate ovarian cancer prevalence. Odds ratio was used to explore risk factors for cancer development.

Results: In our meta-analysis of 20 studies, 31,667 women with Non-EAOC were compared with 2826 women with EAOC across various factors: EOC subtypes, age, parity, menopausal status, FIGO stage, 5-year survival rate, and Ca125 levels. In our study, EAOC exhibited a 7.34% cancer incidence. While clear cell and endometrioid types were more common in EAOC than in the non-EAOC group, the low-grade serous type was the most prevalent malignancy.

Patients with early-stage EAOC have a 1.7 times higher 5-year survival rate compared with non-EAOC groups. EAOC is more common in nulliparous (2.243 times) and premenopausal women (2.169 times), but the CA125 levels are not significantly different between the groups.

Conclusion: Based on data and positive outlook, careful monitoring, considering medical history, and avoiding early surgery are highly recommended in endometriotic patients.

Keywords: Endometriosis, Ovarian neoplasms, Risk factors

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Introduction

Endometriosis is defined as the proliferation of endometrial glands and stroma out of the uterus. This disease affects 3 to 10% of women of childbearing age, 2 to 5% of the postmenopausal age women, and 25 to 80% of infertile women.[1] Despite endometriosis being a benign disease, according to its behavior, such as uncontrolled growth, neo-angiogenesis, local invasion, and distant spreading, it behaves like invasive neoplasms.[2-5] Several studies have reported that patients with endometriosis are at the risk of ovarian cancer, especially the clear cell and endometrioid types.[6-9] Moreover, women with endometriosis have a three-fold chance of clear-cell and a two-fold chance of endometrioid ovarian cancer compared with normal population. The prevalence of endometriosis- associated ovarian cancer (EAOC) has been reported to be between 7 and 13% in surgical specimens.[7,10] In this regard, Sampson was the first to describe the association between endometriosis and ovarian cancer in 1925, followed by whom Scott further defined EAOC. Their proposed criteria, stating that benign endometriosis should be contiguous with malignant tissue, are still used for identifying malignant tumors caused by endometriosis.[11-13] This transformation into malignancy starts from ovarian epithelial cells metaplasia and proliferation in the lining of an atypical endometrioma, followed by a well-defined border line tumor culminating in malignant ovarian cancer as a result.[14] A number of studies have shown that EAOC is a different entity from endometriosis due to its histological subgroup and early and favorable manifestations, while others disagree with this theory. The results of various epidemiological studies on the relationship between endometriosis and ovarian malignancy have not been conclusive so far.[15-18] Since we do not consider endometriosis lesions as precancerous lesions, we prefer the policy of observational and medical treatment for most patients with endometriosis lesion until the end of the reproductive age. Accordingly, it is pivotal to know the risk factors in the transformation of endometriosis lesions into malignancy in order to improve the process of screening and follow-up of these patients.[19-21]

Therefore, this meta-analysis aimed to discover the relationship between the prevalence and prognosis of EAOC in each histological subtype of ovarian cancer. Moreover, this meta-analysis seeks to determine the prevalence, assess the prognosis of EAOC in different histological subtypes of epithelial ovarian cancer (EOC), and compare its risk factors with the non-endometriosis- associated ovarian cancer (non-EAOC) group to enhance disease management across a woman's lifespan.

Materials and Methods

This systematic review was reported based on the PRISMA checklist.

Inclusion criteria

Only studies that met the minimum score on the quality assessment checklist, reported the sample size, and discussed the relationship between ovarian cancer and endometriosis were included in the study.

Exclusion criteria

Papers were excluded if the prevalence of ovarian cancer in endometriosis women was not reported or the sample size was not specified. Additionally, abstracts of seminars without full text, as well as case-reports and studies that did not obtain the minimum required score on the quality assessment checklist were excluded from the study.

Database and search strategies

An electronic databases search was carried out, including PubMed, Science Direct, Scopus, Google Scholar, Cochrane, SID, and Magiran (from 2010 to 2023).

An online search was done for free text keywords, endometriosis" and "ovarian cancer risk factor, rate, percentage with "Or" and "And" operations in the title and abstract of studies. Moreover, in order to increase the sensitivity of the study, we tried to find publications that may not be found through the databases search. To this end, a manual search of the reference list of

Table 1. Quality of studies using National Heart, Lung, and Blood Institute (NHLBI) quality assessment

Study	Was the research question or objective in this paper clearly stated?	Was the study population clearly specified and Defined?	Was the participation rate of eligible persons at least 50%?	Were all the subjects selected or recruited from the same or similar populations?	Was a sample size justification, power description or variance and effect estimates provided?	For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Was the timeframe sufficient, so that one could reasonably expect to see an association between exposure and outcome, if it existed?	For exposures that can vary in amount or level, did the study examine different levels of the exposure?	Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Was the exposure(s) assessed more than once over time?	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Were the outcome assessors blinded to the exposure status of participants?	Was loss to follow-up after baseline 20% or less?	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Summary quality
U Chol Ju et al. 2018[24]	✓	✓	✓	NR	✓	✓	✓	✓	✓	NA	✓	NA	×	✓	F/G
Acein et al. 2015[25]	✓	✓	✓	NR	✓	✓	✓	✓	✓	NA	✓	NA	×	✓	F/G
Bas Esteve et al. 2019[26]	✓	NR	✓	NR	✓	✓	✓	✓	✓	NA	✓	NA	×	✓	Fair
Boyraz et al. 2013[27]	✓	✓	✓	NR	✓	✓	✓	✓	✓	NA	✓	NA	×	✓	F/G
Hermens et al. 2020[6]	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓	NA	×	✓	Good
Kumar et al. 2011[2]	✓	✓	✓	NR	✓	✓	✓	✓	✓	NA	✓	NA	×	✓	F/G
Lim et al. 2010[28]	✓	✓	✓	NR	✓	✓	✓	✓	✓	NA	✓	NA	×	✓	F/G
Mangili et al. 2012[29]	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓	NA	×	✓	Good
Qianwen Li et al. 2019[30]	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓	NA	×	✓	Good
Yan Cai et al. 2019[31]	✓	✓	✓	NR	✓	✓	✓	✓	✓	NA	✓	NA	×	✓	F/G
Shuang et al. 2014[32]	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓	NA	×	✓	Good
Bounous et al. 2016[33]	✓	✓	✓	NR	✓	✓	✓	✓	✓	NA	✓	NA	×	✓	F/G
Son,Joo et al. 2019[34]	✓	✓	✓	NR	✓	✓	✓	✓	✓	NA	✓	NA	×	✓	F/G
Huimin Bai et al. 2016[35]	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓	NA	×	✓	Good
Lin Qiu et al. 2013[36]	✓	✓	✓	NR	✓	✓	✓	✓	✓	NA	✓	NA	×	✓	F/G
Muangtan et al. 2018[37]	✓	✓	✓	NR	✓	✓	✓	✓	✓	NA	✓	NA	×	✓	F/G
Wang et al. 2013[38]	✓	✓	✓	NR	✓	✓	✓	✓	✓	NA	✓	NA	×	✓	F/G
E Sun Paik et al. 2017[39]	✓	✓	✓	✓	✓	✓	✓	✓	✓	NA	✓	NA	×	✓	Good
Tong Ren et al. 2017[40]	✓	✓	✓	✓	NR	✓	✓	✓	✓	NA	✓	NA	×	✓	F/G
Jiaqi Lu et al. 2017[41]	✓	✓	NR	✓	NR	✓	✓	✓	✓	NA	✓	NA	×	✓	Fair

N/A: Not applicable; N/R: Not received; F/G: Fair to good

the retrieved studies was done. Only articles in English language, and articles published from 2010 until September 2023 were included in the study. The search was conducted by two researchers independently, and the third researcher checked the agreement between the retrieved results by the two researchers.

Study selection and data extraction

All articles, documents, and reports were retrieved using advanced search methods. After eliminating duplicate items, irrelevant content was filtered out based on title, abstract, and full-text

examination. The remaining articles and related studies underwent qualitative evaluation. To prevent bias from overlapping publication, researchers reviewed and removed any duplicate studies. Two reviewers independently assessed all articles using the inclusion and exclusion criteria. Data from the articles were summarized by both reviewers, with any discrepancies resolved through the input of a third reviewer.

Data items

This study was conducted to investigate and compare the relationship between the pathological and clinical characteristics, behavior, and prognosis of women who underwent surgical staging for ovarian carcinoma related or unrelated to endometriosis. Therefore, we extracted data on the total number of women who underwent ovarian cancer surgery and the group in which background endometriosis was found in their histopathology slides, and subsequently compared EAOC with the non-EAOC group in terms of: prevalence of different ovarian cancer types, ovarian cancer risk factors, such as age, parity, menopausal status, types of ovarian tumors, and CA125 level in both groups. Next, the International Federation of Gynecology and Obstetrics (FIGO) staging, and 5-year survival were compared between the two groups and thoroughly investigated. Finally, the results were classified and expressed in the form of odds ratio for better understanding.

Data analysis

The standard error of ovarian cancer in endometriosis women in each study was calculated using binominal distribution formula. The results were reported with 95% confidence interval (CI).[22]

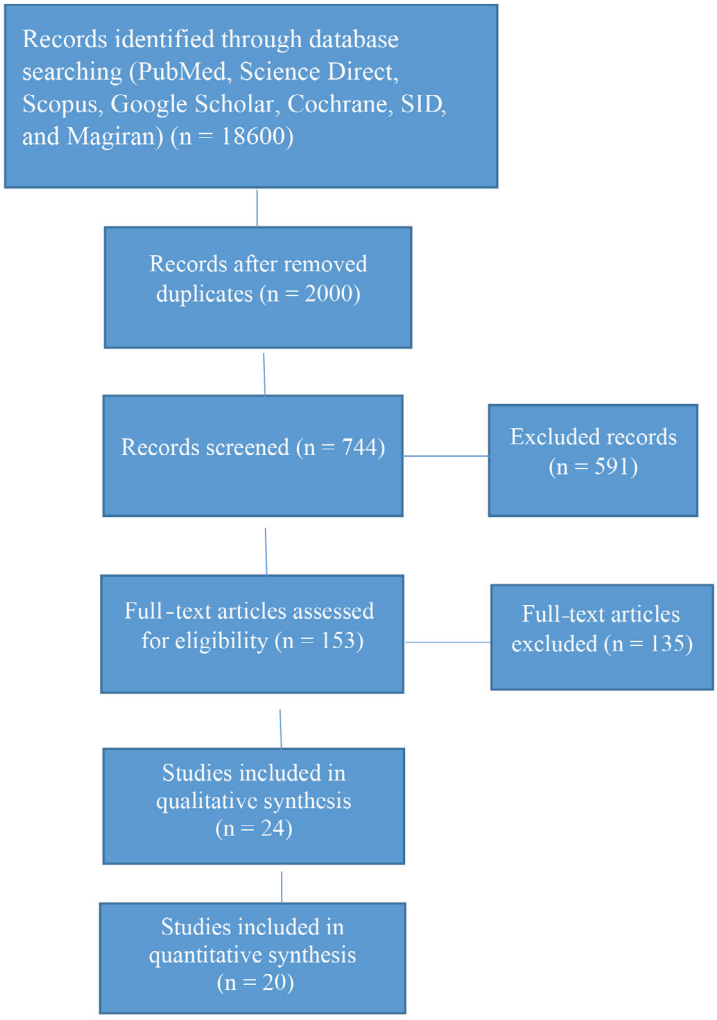

Figure 1. The flowchart outlines the process of searching and reviewing papers in accordance with PRISMA guidelines.

Table 2. Main characteristics of the included studies on EOC with or without synchronous endometriosis, its prognostic factor, pathological detection methods and outcomes

Study	Country	Study type	Sample size	Study question	Definition of endometriosis type	Histological	Adjusted factors	Outcome
U chol ju et al. 2018[24]	Korea	Retrospective	129	Clinical and prognostic features of ovarian CCC and EC were compared between women with and without endometriosis.	EAOC was defined: as any of the following ovarian cancer with endometriosis identified histologically in the same ovary, endometriosis in one ovary, and ovarian cancer in the contralateral ovary, or ovarian cancer with extra-ovarian pelvic endometriosis.	OCCC, EOC	Age, CA 125, FIGO Stage Menopausal status, Gravidity	5-year survival
Acién et al. 2015[25]	Spain	Observational cohort	192	Determining the prevalence of endometriosis in EOC.	EAOC was defined by the presence of ovarian cancer and endometriosis in the same or contralateral ovary or extraovarian pelvic endometriosis. So, endometriosis was identified when the tissue resembling endometrial stroma surrounding epithelial glands was present in ovaries or peritoneum. Besides, atypical endometriosis was considered according to the criteria from Thomas and Campbell.	Serous, mucinous, OCCC, EOC, others	Age, CA 125, Stage, Menopausal status,Gravidity, 5-year survival, concomitant endometrial cancer	5-year survival
Bas Esteve et al. 2019[26]	Spain	Retrospective	341	To compare the histological pattern, survival and immunohistochemical data between women with and without endometriosis.	EAOC was defined by the presence of ovarian cancer and endometriosis in the same or contralateral ovary or extraovarian pelvic endometriosis. So, endometriosis was identified when the tissue resembling endometrial stroma surrounding epithelial glands was present in ovaries or peritoneum Besides, atypical endometriosis was considered according to the criteria from Thomas and Campbell.	Serous, mucinous, OCCC, EOC, others	Age, CA 125, FIGO Stage, Menopausal status, Gravidity, 5 year survival, concomitant endometrial cancer	5-year survival
Boyraz et al. 2013[27]	Turkey	Retrospective	1086	To evaluate the cases of ovarian carcinoma associated with endometriosis.	Pathology reports of 1086 patients who underwent surgical staging for ovarian carcinoma were analyzed retrospectively for the presence of histologically documented endometriosis.	Serous, mucinous, OCCC, EOC, others	Age, Stage, Menopausal status	N/R
Hermens et al. 2020[6]	Netherland	Retrospective	30440	To elucidate the role of endometriosis in ovarian cancer prognosis.	Select all women with any histologic diagnosis of endometriosis, including adenomyosis, between 1990 and 2015.	Serous, mucinous, OCCC, EOC, others	Age, CA 125, FIGO Stage, Menopausal status, Gravidity	5-year survival
Kumar et al. 2011[2]	Canada	Retrospective	226	To evaluate the prognosis of ovarian cancer arising in e ndometriosis.	Pathology reports of patients who underwent surgical staging for ovarian carcinoma were analyzed retrospectively by two of the authors for the presence of histologically documented endometriosis.	Serous, mucinous, OCCC, EOC, others	Age, FIGO Stage, 5-year survival	5-year survival
Lim et al. 2010[28]	Korea	Retrospective	221	Clinical characteristics and presenting symptoms of EOC with concurrent endometriosis	The presence of endometriosis was determined from H&E-stained sections of resected specimens. The coexistence of endometriosis was diagnosed by confirming the presence of ectopic endometrial glands or stroma.	EOC	Age, FIGO Stage, Menopausal status, concomitant endometrial cancer	NR
Mangili et al. 2012[29]	Italy	Retrospective	65	To evaluate the clinical and pathological characteristics of the patients with endometrioid ovarian cancer with and without endometriosis.	All pathologic specimens of patients who underwent surgical staging for endometrioid ovarian carcinoma were analyzed retrospectively for the presence of histologically documented endometriosis.	EOC	Age, CA 125, FIGO Stage, Menopausal status, concomitant endometrial cancer 5-year survival.	5-year survival

N/R: Not received; OCCC: Ovarian clear cell carcinoma; CCC: Clear cell carcinoma; EOC: Epithelial ovarian cancer; EAOC: Endometriosis-associated ovarian cancer; Non-EAOC: Non-endometriosis associated ovarian cancer; OEC: Ovarian endometrioid carcinoma; OS: Overall survival; EOC-E: EOC coexisting with endometriosis; EC: Endometrioid carcinoma; H&E: Hematoxylin and eosin; I^2: Data heterogeneity; FIGO: The International Federation of Gynecology and Obstetrics

Table 2. Main characteristics of the included studies on EOC with or without synchronous endometriosis, its prognostic factor, pathological detection methods and outcomes (continued)

Study	Country	Study type size	Sample	Study question	Definition of endometriosis type	Histological	Adjusted factors	Outcome
Qianwen li et al. 2019[30]	China	Retrospective	128	To evaluate the clinicopathological features and chemotherapy response of EAOC compared with non-EAOC.	All pathologic specimens of patients who underwent surgical staging for ovarians carcinoma were analyzed retrospectively for the presence of histologically documented endometriosis.	OCCC, EOC	Age, FIGO stage, Menopausal status, 5-year survival	5-year survival
Yan cai et al. 2019[31]	China	Retrospective	94	To investigate the clinicopathological features and prognostic value of endometriosis in young patients with OEC and OCCC.	EAOC was defined as the presence of ovarian cancer and endometriosis identified histologically in the same ovary or the presence of ovarian cancer in one ovary with endometriosis in the contralateral ovary or extraovarian pelvic endometriosis.	OCCC, EOC, mixed type	Age, FIGO stage, Gravidity, 5-year survival, concomitant endometrial cancer	5-year survival
Shuang et al. 2014[32]	China	Retrospective	210	To analyze and compare the clinicopathological features and prognosis of OCCC with or without endometriosis.	Microscopic slides were reviewed and confirmed by a single experienced gynecologic pathologist (Dr. You). EAOC was defined as follows: [1] presence of CCC and endometriosis in the same ovary, [2] presence of endometriosis in one ovary and of CCC in the contralateral ovary, [3] presence of CCC and extraovarian endometriosis.	OCCC	Age, CA 125, FIGO stage, Menopausal status, 5-year survival	5-year survival
Bounous et al. 2016[33]	Italy	Retrospective	203	To evaluate the incidence of EAOC and compare clinicopathological characteristics and OS between patients with EAOC and those with ovarian cancer not associated with endometriosis.	Definition of EAOC according to the Van Gorp classification (1), including endometriosis concurrent with ovarian cancer in the same ovary (category A), ovarian cancer with endometriosis in the same ovary but without histological proof of transition all three categories: (category B); ovarian cancer with concomitant endometriosis at any other location in the pelvis (category C).	Serous, mucinous, OCCC, EOC, others	Age, FIGO stage, Gravidity	NR
Son, Joo-Hyuk et al. 2019[34]	Korea	Retrospective	50	To analyze the clinical features of CCC in relation to endometriosis and to determine an appropriate surveillance strategy for the early detection of malignant transformation of endometrioma in asymptomatic patients.	Pathology reports of the patients who underwent surgical staging for clear cell ovarian carcinoma were analyzed retrospectively for the presence of histologically documented endometriosis.	OCCC	Age, FIGO stage	NR
Huimin Bai et al. 2016[35]	China	Retrospective	237	To investigate the prognostic value of endometriosis in patients with stage I OCCC.	EAOC was defined as the co-existence of OCCC and endometriosis in the same and/or contralateral ovary and/or the co-existence of OCCC and extra ovarian endometriosis	OCCC	FIGO stage, Menopausal status, 5-year survival	5-year survival
Lin Qiu et al. 2013[36]	China	Retrospective	226	To explore the association between the menopausal status EOC and endometriosis	EOC concomitant with pelvic endometriosis" was defined as follows: (1) the presence of ovarian cancer and endometriosis identified histologically in the same ovary; (2) the presence of endometriosis in one ovary and the presence of ovarian cancer in the contralateral ovary; or (3) the presence of ovarian cancer and extraovarian pelvic endometriosis.	Serous, mucinous, OCCC, EOC, others	Crude	NR
Muangtan et al.2018[37]	Thailand	Retrospective	172	To determine any association between the Menopausal status, and EOC-E.	All pathologic specimens of patients who underwent surgical staging for ovarian carcinoma were analyzed retrospectively for the presence of histologically documented endometriosis.	Serous, mucinous, OCCC, EOC, others	Age, CA 125, FIGO stage, Menopausal status Gravidity	NR

N/R: Not received; OCCC: Ovarian clear cell carcinoma; CCC: Clear cell carcinoma; EOC: Epithelial ovarian cancer; EAOC: Endometriosis-associated ovarian cancer; Non-EAOC: Non-endometriosis associated ovarian cancer; OEC: Ovarian endometrioid carcinoma; OS: Overall survival; EOC-E: EOC coexisting with endometriosis; EC: Endometrioid carcinoma; H&E: Hematoxylin and eosin; I^2: Data heterogeneity; FIGO: The International Federation of Gynecology and Obstetrics

Table 2. Main characteristics of the included studies on EOC with or without synchronous endometriosis, its prognostic factor, pathological detection methods and outcomes (continued)

Study	Country	Study type size	Sample	Study question	Definition of endometriosis type	Histological	Adjusted factors	Outcome
Muangtan et al.2018[37]	Thailand	Retrospective	172	To determine any association between the Menopausal status, and EOC-E.	All pathologic specimens of patients who underwent surgical staging for ovarian carcinoma were analyzed retrospectively for the presence of histologically documented endometriosis.	Serous, mucinous, OCCC, Menopausal EOC, others Gravidity	Age, CA 125, FIGO stage, status	NR
Wang et al. 2013[38]	China	Retrospective	226	To analyze and compare the clinicopathological features of ovarian carcinoma with or without endometriosis.	EAOC was defined as follows: (1) presence of ovarian cancer and endometriosis identified histologically in the same ovary; (2) presence of endometriosis in one ovary and that of ovarian cancer in the contralateral ovary; or (3) the presence of ovarian cancer and extraovarian pelvic endometriosis	Serous, mucinous, OCCC, EOC, others	Age, CA 125, FIGO stage, Menopausal status	NR
E Sun Paik et al. 2017[39]	Korea	Retrospective	224	To compare outcomes of patients according to the presence of cancer arising from endometriosis in OCCC and EC.	Based on the Sampson and Scott criteria: 1) the presence of both benign and neoplastic endometrial tissues in the tumor, 2) histological findings compatible with endometrial origin, 3) the discovery of no other primary tumor sites, and 4) morphologic demonstration of a continuum between benign and malignant epithelium.	OCCC, EOC FIGO stage, Menopausal status, Gravidity	Age, CA 125,	NR
Tong Ren et al. 2017[40]	China	Retrospective	304	To explore the Clinicopathological characteristics and possible prognostic factors among women with EOC with or without concurrent endometriosis.	EOC with concurrent endometriosis as the presence of ovarian cancer and endometriosis identified histologically in the same ovary, the presence of endometriosis in one ovary and of ovarian cancer in the contralateral ovary, or the presence of ovarian cancer and extraovarian pelvic endometriosis	OCCC, EOC FIGO stage, Menopausal status, Gravidity	Age, CA 125,	NR
Jiaqi lu et al. 2017[41]	China	Retrospective	196	To assess the association between endometriosis and the prognosis in patients with ovarian cancer.	Of the specimens were histologically positive for ovarian cancer arising in endometriosis by H&E staining, reconfirmation of all samples by CD10 staining.	OCCC, EOC FIGO stage, Menopausal status, Gravidity	Age, CA 125,	5-year survival

N/R: Not received; OCCC: Ovarian clear cell carcinoma; CCC: Clear cell carcinoma; EOC: Epithelial ovarian cancer; EAOC: Endometriosis-associated ovarian cancer; Non-EAOC: Non-endometriosis associated ovarian cancer; OEC: Ovarian endometrioid carcinoma; OS: Overall survival; EOC-E: EOC coexisting with endometriosis; EC: Endometrioid carcinoma; H&E: Hematoxylin and eosin; I^2: Data heterogeneity; FIGO: The International Federation of Gynecology and Obstetrics

Cochran's Q test and the I2 index were used to report heterogeneity. An I2 index value of 0%-50% indicated low heterogeneity, and a value >50% demonstrated high heterogeneity.[22] If I2 > 50%, the random effect was used to interpret the results. The data were analyzed using Med-Calc (18.9.1 version) software.

Random effect model was employed for estimating the prevalence of ovarian cancer due to the heterogeneity of the papers. The point prevalence of ovarian cancer among endometriosis women was calculated with 95% CI and forest plot, in which the size of the square represents the weight of each study and its booth sides' lines represent a 95% CI.

To investigate malignant transformation-related risk factors in the EAOC group compared with the Non-EAOC group, we used the odds ratio.

Quality assessment of the studies

To assess the methodological quality of each article included in this study, the US National Institute of Health, National Heart, Lung, and Blood Institute quality assessment tool for observational cohort and cross-sectional studies was used.[23] This tool measures 14 different criteria used to give each study an overall quality rating of good, fair, or poor. All articles included in this study had fair to good quality. The results according to the mentioned checklist are summarized in table 1.

Table 3. The prevalence of different types of EOCs associated with endometriosis

Endometriosis related ovarian cancer	Sample size	Incidence rate (%)	95% CI	Weight (%) Fixed	Weight (%) Random	I^2	Sig. diff
Study (serous carcinoma)							
Acién et al. 2015	192	1.042	0.126 to 3.712	0.58	10.08	89.68	< 0.0001
Bas Esteve et al. 2019	341	0.880	0.182 to 2.549	1.03	11.46		
Boyraz et al. 2013	1086	0.552	0.203 to 1.199	3.28	13.03		
Kumar et al. 2011	226	10.177	6.561 to 14.879	0.69	10.52		
Muangtan et al. 2018	172	4.070	1.652 to 8.205	0.52	9.77		
Wang et al. 2013	226	1.327	0.275 to 3.830	0.69	10.52		
Bounous et al 2016	203	8.374	4.954 to 13.070	0.62	10.23		
Lin Qiu et al. 2013	226	1.327	0.275 to 3.830	0.69	10.52		
Hermens et al. 2020	30440	2.280	2.115 to 2.454	91.91	13.88		
Total (fixed effects)	33112	2.247	2.090 to 2.413	100.00	100.00		
Study (mucinous carcinoma)							
Acién et al. 2015	192	0.521	0.0132 to 2.868	0.59	7.84	51.34	0.055
Bas Esteve et al. 2019	341	1.760	0.648 to 3.790	1.05	11.85		
Boyraz et al. 2013	1086	0.368	0.100 to 0.940	3.33	21.71		
Kumar et al. 2011	226	1.770	0.484 to 4.469	0.69	8.87		
Muangtan et al. 2018	172	1.163	0.141 to 4.137	0.53	7.19		
Bounous et al. 2016	203	1.970	0.539 to 4.968	0.62	8.18		
Hermens et al. 2020	30440	0.749	0.655 to 0.852	93.19	34.37		
Total (fixed effects)	32660	0.763	0.672 to 0.864	100.00	100.00		
Study (clear cell carcinoma)							
Acién et al. 2015	192	1.562	0.323 to 4.498	0.56	5.57	98.52	< 0.0001
Bas Esteve et al. 2019	341	2.346	1.018 to 4.570	0.99	5.65		
Boyraz et al. 2013	1086	1.565	0.914 to 2.495	3.13	5.73		
Kumar et al. 2011	226	3.982	1.837 to 7.425	0.65	5.60		
Muangtan et al. 2018	172	6.395	3.235 to 11.155	0.50	5.54		
Wang et al. 2013	226	3.540	1.540 to 6.855	0.65	5.60		
Qianwen li et al. 2019	128	14.063	8.552 to 21.311	0.37	5.47		
Yan Cai et al. 2019	94	22.340	14.393 to 32.100	0.27	5.37		
Shuang et al. 2014	210	37.619	31.046 to 44.547	0.61	5.58		
Bounous et al. 2016	203	2.463	0.804 to 5.654	0.59	5.58		
Son,Joo-Hyuk et al. 2019	50	70.000	55.392 to 82.138	0.15	5.07		
Huimin Bai et al. 2016	237	44.304	37.875 to 50.877	0.69	5.60		
Lin Qiu et al. 2013	226	3.540	1.540 to 6.855	0.65	5.60		
Hermens et al. 2020	30440	1.110	0.996 to 1.235	87.72	5.77		
U Chul Ju et al. 2018	129	11.628	6.656 to 18.452	0.37	5.47		
E Sun Paik et al. 2017	224	9.375	5.897 to 13.973	0.65	5.59		
Tong ren et al. 2017	304	12.171	8.716 to 16.384	0.88	5.64		
Jiaqi lu et al. 2017	196	24.490	18.643 to 31.126	0.57	5.57		
Total (fixed effects)	34684	1.626	1.495 to 1.764	100.00	100.00		
Study (endometrioid carcinoma)							
Acién et al. 2015	192	2.604	0.851 to 5.972	0.56	5.89	96.72	< 0.0001
Bas Esteve et al. 2019	341	5.572	3.388 to 8.565	0.99	6.09		
Boyraz et al. 2013	1086	1.381	0.775 to 2.268	3.15	6.28		
Kumar et al. 2011	226	2.655	0.980 to 5.689	0.66	5.95		
Muangtan et al. 2018	172	4.651	2.029 to 8.959	0.50	5.83		
Wang et al. 2013	226	2.655	0.980 to 5.689	0.66	5.95		
Lim et al. 2010	221	37.104	30.721 to 43.838	0.64	5.94		
Mangili et al. 2012	65	32.308	21.233 to 45.055	0.19	5.13		
Qianwen Li et al. 2019	128	12.500	7.317 to 19.504	0.37	5.67		
Yan Cai et al. 2019	94	17.021	10.054 to 26.165	0.28	5.45		
Bounous et al .2016	203	6.404	3.454 to 10.702	0.59	5.91		
Lin Qiu et al 2013	226	2.655	0.980 to 5.689	0.66	5.95		
Hermens et al. 2020	30440	1.751	1.607 to 1.905	88.26	6.37		
U Chul Ju et al. 2018	129	11.628	6.656 to 18.452	0.38	5.67		
E Sun Paik et al. 2017	224	8.929	5.539 to 13.453	0.65	5.95		
Tong Ren et al. 2017	304	10.526	7.312 to 14.534	0.88	6.06		
Jiaqi Lu et al. 2017	196	4.592	2.121 to 8.538	0.57	5.89		
Total (fixed effects)	34473	2.110	1.961 to 2.267	100.00	100.00		
Study (mixed type carcinoma)							
Acién et al. 2015	192	4.687	2.166 to 8.712	0.60	14.84	85.38	< 0.0001
Boyraz et al. 2013	1086	0.276	0.0570 to 0.805	3.38	21.44		
Muangtan et al. 2018	172	1.744	0.361 to 5.012	0.54	14.23		
Yan Cai et al. 2019	94	3.191	0.663 to 9.045	0.30	10.71		
Bounous et al .2016	203	2.956	1.092 to 6.322	0.63	15.15		
Hermens et al. 2020	30440	0.611	0.527 to 0.705	94.56	23.63		
Total (fixed effects)	32187	0.636	0.552 to 0.729	100.00	100.00		

EOC: Epithelial ovarian cancer; CI: Confidence interval; Sig diff: Significant difference; I^2: Data heterogeneity

Table 4. The incidence rate of EOCs associated with endometriosis based on the parity, menopausal status, FIGO staging, and also 5 years survival

Endometriosis related ovarian cancer	Sample size	Incidence rate (%)	95% CI	Weight (%)		I^2	Sig. diff
				Fixed	Random		
Study (nulliparous)							
Acién et al. 2015	192	5.208	2.526 to 9.370	14.71	16.71	86.02	<0.0001
Bas Esteve et al. 2019	341	5.279	3.158 to 8.214	26.07	17.89		
Muangtan et al. 2018	172	9.302	5.411 to 14.667	13.19	16.42		
Yan Cai et al. 2019	94	24.468	16.186 to 34.418	7.24	14.45		
Bounous et al. 2016	203	5.911	3.091 to 10.098	15.55	16.84		
Tong Ren et al. 2017	304	3.289	1.588 to 5.966	23.25	17.69		
Total (fixed effects)	1306	6.468	5.198 to 7.937	100.00	100.00		
Study (multiparous)							
Acién et al. 2015	192	5.208	2.526 to 9.370	14.71	16.71	90.06	<0.0001
Bas Esteve et al. 2019	341	5.279	3.158 to 8.214	26.07	17.54		
Muangtan et al. 2018	172	8.721	4.963 to 13.976	13.19	16.50		
Yan Cai et al. 2019	94	18.085	10.903 to 27.369	7.24	15.03		
Bounous et al. 2016	203	16.256	11.462 to 22.065	15.55	16.81		
Tong Ren et al. 2017	304	19.408	15.115 to 24.308	23.25	17.40		
Total (fixed effects)	1306	11.072	9.425 to 12.896	100.00	100.00		
Study (pre-menopause)							
Acién et al. 2015	192	5.729	2.894 to 10.020	5.81	8.35	96.57	<0.0001
Bas Esteve et al. 2019	341	5.865	3.619 to 8.913	10.29	8.52		
Boyraz et al. 2013	1086	1.934	1.201 to 2.941	32.71	8.67		
Muangtan et al. 2018	172	6.395	3.235 to 11.155	5.21	8.31		
Wang et al. 2013	226	5.752	3.098 to 9.636	6.83	8.41		
Lim et al. 2010	221	25.792	20.158 to 32.088	6.68	8.40		
Mangili et al. 2012	65	9.231	3.463 to 19.017	1.99	7.69		
Qianwen li et al. 2019	128	8.594	4.368 to 14.856	3.88	8.17		
Shuang et al. 2014	210	26.190	20.381 to 32.686	6.35	8.38		
Huimin Bai et al. 2016	237	30.802	24.987 to 37.105	7.16	8.42		
U Chul Ju et al. 2018	129	13.953	8.484 to 21.153	3.91	8.17		
Tong Ren et al. 2017	304	17.434	13.341 to 22.176	9.18	8.49		
Total (fixed effects)	3311	8.806	7.864 to 9.822	100.00	100.00		
Study (post-menopause)							
Acién et al. 2015	192	4.687	2.166 to 8.712	5.81	8.36	91.56	<0.0001
Bas Esteve et al. 2019	341	4.692	2.705 to 7.508	10.29	8.77		
Boyraz et al. 2013	1086	2.210	1.421 to 3.270	32.71	9.18		
Muangtan et al .2018	172	11.628	7.249 to 17.386	5.21	8.25		
Wang et al. 2013	226	1.770	0.484 to 4.469	6.83	8.50		
Lim et al. 2010	221	10.407	6.713 to 15.206	6.68	8.48		
Mangili et al. 2012	65	23.077	13.529 to 35.190	1.99	6.91		
Qianwen Li et al. 2019	128	17.969	11.745 to 25.732	3.88	7.93		
Shuang et al. 2014	210	11.429	7.461 to 16.526	6.35	8.44		
Huimin Bai et al. 2016	237	13.502	9.422 to 18.523	7.16	8.53		
U Chul Ju et al. 2018	129	9.302	4.900 to 15.686	3.91	7.94		
Tong Ren et al. 2017	304	5.263	3.038 to 8.406	9.18	8.71		
Total (fixed effects)	3311	5.901	5.124 to 6.756	100.00	100.00		
Study (FIGO stage 1,2)							
Acién et al. 2015	192	6.771	3.654 to 11.300	0.56	5.59	98.08	<0.0001
Bas Esteve et al. 2019	341	8.504	5.769 to 11.985	0.99	5.70		
Boyraz et al. 2013	1086	2.486	1.645 to 3.597	3.14	5.80		
Kumar et al. 2011	226	8.850	5.489 to 13.336	0.66	5.62		
Muangtan et al. 2018	172	8.140	4.521 to 13.280	0.50	5.56		
Wang et al. 2013	226	7.522	4.443 to 11.771	0.66	5.62		
Lim et al. 2010	221	28.507	22.654 to 34.947	0.64	5.62		
Mangili et al. 2012	65	20.000	11.102 to 31.769	0.19	5.14		
Qianwen Li et al. 2019	128	24.219	17.087 to 32.581	0.37	5.47		
Yan Cai et al. 2019	94	27.660	18.929 to 37.846	0.27	5.34		
Shuang et al. 2014	210	29.524	23.445 to 36.191	0.61	5.61		
Bounous et al. 2016	203	7.882	4.572 to 12.484	0.59	5.60		
Son,Joo-Hyuk et al. 2019	50	50.000	35.527 to 64.473	0.15	4.97		
Huimin Bai et al. 2016	237	44.304	37.875 to 50.877	0.69	5.63		
Hermens et al. 2020	30440	4.162	3.941 to 4.393	87.90	5.84		
E Sun Paik et al. 2017	224	16.964	12.293 to 22.533	0.65	5.62		
Tong Ren et al. 2017	304	20.066	15.711 to 25.015	0.88	5.68		
Jiaqi Lu et al. 2017	196	26.020	20.029 to 32.753	0.57	5.59		
Total (fixed effects)	3461	4.962	4.736 to 5.196	100.00	100.00		

EOC: Epithelial ovarian cancer; FIGO: the International Federation of Gynecology and Obstetrics; CI: Confidence interval; Sig diff: Significant difference; I^2: Data heterogeneity

Table 4. The incidence rate of EOCs associated with endometriosis based on the parity, menopausal status, FIGO staging, and also 5 years survival (continued)

Endometriosis related ovarian cancer	Sample size	Incidence rate (%)	95% CI	Weight (%)		I^2	Sig. diff
				Fixed	Random		
Study (FIGO stage 3,4)							
Acién et al. 2015	192	3.646	1.478 to 7.367	0.56	6.33	92.10	<0.0001
Bas Esteve et al. 2019	341	1.760	0.648 to 3.790	1.00	6.84		
Boyraz et al. 2013	1086	1.657	0.985 to 2.607	3.18	7.37		
Kumar et al. 2011	226	9.292	5.844 to 13.853	0.66	6.50		
Muangtan et al. 2018	172	9.884	5.864 to 15.353	0.51	6.21		
Lim et al. 2010	221	8.597	5.256 to 13.100	0.65	6.47		
Mangili et al. 2012	65	12.308	5.466 to 22.819	0.19	4.76		
Qianwen Li et al. 2019	128	2.344	0.486 to 6.697	0.38	5.83		
Yan Cai et al. 2019	94	14.894	8.389 to 23.725	0.28	5.38		
Shuang et al. 2014	210	8.095	4.786 to 12.645	0.62	6.42		
Bounous et al. 2016	203	14.286	9.781 to 19.868	0.60	6.39		
Son,Joo-Hyuk et al. 2019	50	20.000	10.030 to 33.718	0.15	4.28		
Hermens et al. 2020	30440	2.178	2.017 to 2.348	89.09	7.63		
E Sun Paik et al. 2017	224	1.339	0.277 to 3.864	0.66	6.49		
Tong Ren et al. 2017	304	2.632	1.143 to 5.119	0.89	6.75		
Jiaqi Lu et al. 2017	196	3.571	1.448 to 7.220	0.58	6.35		
Total (fixed effects)	34152	2.386	2.227 to 2.553	100.00	100.00		
Study (5 years Survival)							
Acién et al. 2015	20	31.000	12.573 to 55.285	4.42	9.33	92.61	<0.0001
Bas Esteve et al. 2019	36	30.600	16.382 to 48.153	7.79	9.97		
Kumar et al. 2011	42	62.000	45.732 to 76.509	9.05	10.10		
Mangili et al. 2012	21	44.000	22.738 to 67.013	4.63	9.40		
Qianwen Li et al. 2019	34	67.800	49.630 to 82.732	7.37	9.92		
Yan Cai et al. 2019	40	85.800	71.125 to 94.790	8.63	10.06		
Shuang et al. 2014	79	70.200	58.857 to 79.974	16.84	10.48		
Huimin Bai et al. 2016	105	97.500	92.397 to 99.556	22.32	10.60		
U Chul Ju et al. 2018	30	80.300	61.774 to 92.479	6.53	9.80		
Jiiaqi Lu et al. 2017	58	86.600	75.090 to 94.120	12.42	10.32		
Total (fixed effects)	465	75.964	71.861 to 79.740	100.00	100.00		

EOC: Epithelial ovarian cancer; FIGO: the International Federation of Gynecology and Obstetrics; CI: Confidence interval; Sig diff: Significant difference; I^2: Data heterogeneity

Results

Study selection

Through the initial online search of the databases, a total of 18,600 studies were found, out of which 15,600 were removed after limiting the search. Out of the remaining 2000 studies, 1256 were removed due to overlapping searched databases. After reviewing the titles and abstracts of 744 studies, 591 were identified to be irrelevant, while the remaining 153 papers were selected to be investigated thoroughly. Subsequently, 135 papers were removed from the study due to irrelevancy. The remaining 24 studies, which were found in manual search, were then assessed based on the quality assessment checklist. Based on the inclusion and exclusion criteria, four studies were removed and 20 studies were found to be appropriate for the current meta-analysis (Figure 1).

Study characteristics

These 20 papers were published from 2010 to 2023. Furthermore, all the data about the authors, studies, types of ovarian cancer related or non-related to endometriosis, risk factors, and outcomes of the studies are presented in table 2.[2,6,24-41]

Analytical results

This study was conducted to investigate and compare the relationship between the pathological and clinical characteristics, behavior, and prognosis of women who underwent surgical staging for ovarian carcinoma related or unrelated to endometriosis. Among 31,667 women of ovarian cancer without endometriosis, 2,826 were diagnosed with ovarian carcinoma related to endometriosis based on their pathologic slides.

Accordingly, the prevalence of different ovarian cancer types, and the ovarian cancer risk factors, such as age, parity, menopausal status, types of ovarian tumors, and CA125 level in both groups, were initially investigated. Then, FIGO staging, and 5-year survival were compared between the two groups and thoroughly investigated. Finally,

Table 5. The prevalence of different types of EOCs non-associated with endometriosis

Non-endometriosis related ovarian cancer	Sample size	Incidence rate (%)	95% CI	Weight (%) Fixed	Weight (%) Random	I^2	Sig. diff
Study (serous carcinoma)							
Acién et al. 2015	192	46.354	39.145 to 53.677	0.58	10.68	96.88	<0.0001
Bas Esteve et al. 2019	341	42.815	37.499 to 48.257	1.03	11.29		
Boyraz et al. 2013	1086	51.197	48.178 to 54.209	3.28	11.90		
Kumar et al. 2011	226	65.487	58.895 to 71.666	0.69	10.88		
Muangtan et al. 2018	172	25.581	19.244 to 32.781	0.52	10.53		
Wang et al. 2013	226	66.372	59.807 to 72.501	0.69	10.88		
Bounous et al .2016	203	40.394	33.583 to 47.490	0.62	10.75		
Lin Qiu et al. 2013	226	66.372	59.807 to 72.501	0.69	10.88		
Hermens et al. 2020	30440	43.160	42.603 to 43.719	91.91	12.19		
Total (fixed effects)	33112	43.797	43.262 to 44.334	100.00	100.00		
Study (musinous carcinoma)							
Acién et al. 2015	192	18.750	13.491 to 25.000	0.58	10.46	93.67	<0.0001
Bas Esteve et al. 2019	341	20.235	16.099 to 24.896	1.03	11.37		
Boyraz et al. 2013	1086	16.759	14.584 to 19.116	3.28	12.31		
Kumar et al. 2011	226	11.947	8.023 to 16.904	0.69	10.76		
Muangtan et al. 2018	172	16.279	11.098 to 22.661	0.52	10.25		
Wang et al. 2013	226	7.522	4.443 to 11.771	0.69	10.76		
Bounous et al. 2016	203	4.433	2.047 to 8.249	0.62	10.57		
Lin Qiu et al. 2013	226	7.522	4.443 to 11.771	0.69	10.76		
Hermens et al. 2020	30440	8.968	8.650 to 9.295	91.91	12.78		
Total (fixed effects)	33112	9.345	9.034 to 9.664	100.00	100.00		
Study (clear cell carcinoma)							
Acién et al. 2015	192	3.125	1.155 to 6.677	0.56	5.57	98.75	<0.0001
Bas Esteve et al. 2019	341	4.692	2.705 to 7.508	0.99	5.64		
Boyraz et al. 2013	1086	6.077	4.731 to 7.667	3.13	5.70		
Kumar et al. 2011	226	1.770	0.484 to 4.469	0.65	5.59		
Muangtan et al. 2018	172	5.233	2.420 to 9.700	0.50	5.55		
Wang et al. 2013	226	6.195	3.428 to 10.175	0.65	5.59		
Qianwen Li Et al. 2019	128	29.687	21.940 to 38.401	0.37	5.48		
Yan Cai et al. 2019	94	24.468	16.186 to 34.418	0.27	5.40		
Shuang et al. 2014	210	62.381	55.453 to 68.954	0.61	5.58		
Bounous et al. 2016	203	4.926	2.387 to 8.873	0.59	5.57		
Son,Joo-Hyuk et al. 2019	50	30.000	17.862 to 44.608	0.15	5.14		
Huimin Bai et al. 2016	237	55.696	49.123 to 62.125	0.69	5.60		
Lin Qiu et al. 2013	226	6.195	3.428 to 10.175	0.65	5.59		
Hermens et al. 2020	30440	2.789	2.607 to 2.980	87.72	5.73		
u Chul Ju et al. 2018	129	17.829	11.651 to 25.542	0.37	5.49		
E Sun Paik et al. 2017	224	29.018	23.165 to 35.436	0.65	5.59		
Tong Ren et al. 2017	304	14.474	10.718 to 18.939	0.88	5.63		
Jiaqi Lu et al. 2017	196	21.939	16.355 to 28.391	0.57	5.57		
Total (fixed effects)	34684	3.655	3.460 to 3.858	100.00	100.00		
Study (endometrioid carcinoma)							
Acién et al. 2015	192	3.125	1.155 to 6.677	0.56	5.57	98.59	<0.0001
Bas Esteve et al. 2019	341	4.692	2.705 to 7.508	0.99	5.64		
Boyraz et al. 2013	1086	6.077	4.731 to 7.667	3.13	5.70		
Kumar et al. 2011	226	1.770	0.484 to 4.469	0.65	5.59		
Muangtan et al. 2018	172	5.233	2.420 to 9.700	0.50	5.55		
Wang et al. 2013	226	6.195	3.428 to 10.175	0.65	5.59		
Qianwen Li et al. 2019	128	29.687	21.940 to 38.401	0.37	5.48		
Yan Cai et al. 2019	94	24.468	16.186 to 34.418	0.27	5.40		
Shuang et al. 2014	210	62.381	55.453 to 68.954	0.61	5.58		
Bounous et al. 2016	203	4.926	2.387 to 8.873	0.59	5.57		
Son,Joo-Hyuk et al. 2019	50	30.000	17.862 to 44.608	0.15	5.14		
Huimin Bai et al. 2016	237	55.696	49.123 to 62.125	0.69	5.60		
Lin Qiu et al. 2013	226	6.195	3.428 to 10.175	0.65	5.59		
Hermens et al. 2020	30440	2.789	2.607 to 2.980	87.72	5.73		
U Chul Ju et al. 2018	129	17.829	11.651 to 25.542	0.37	5.49		
E Sun Paik et al. 2017	224	29.018	23.165 to 35.436	0.65	5.59		
Tong Ren et al. 2017	304	14.474	10.718 to 18.939	0.88	5.63		
Jiaqi Lu et al. 2017	196	21.939	16.355 to 28.391	0.57	5.57		
Total (fixed effects)	34684	3.655	3.460 to 3.858	100.00	100.00		
Study (mixed carcinoma)							
Acién et al. 2015	192	9.375	5.651 to 14.412	0.59	11.05	99.00	<0.0001
Bas Esteve et al. 2019	341	14.370	10.823 to 18.549	1.04	11.20		
Boyraz et al. 2013	1086	8.379	6.800 to 10.188	3.30	11.34		

EOC: Epithelial ovarian cancer; CI: Confidence interval; Sig diff: Significant difference; I^2: Data heterogeneity

Table 5. The prevalence of different types of EOCs non-associated with endometriosis (continued)

Non-endometriosis related ovarian cancer	Sample size	Incidence rate (%)	95% CI	Weight (%)		I^2	Sig. diff
				Fixed	Random		
Muangtan et al. 2018	172	20.349	14.602 to 27.147	0.52	11.01		
Wang et al. 2013	226	7.522	4.443 to 11.771	0.69	11.10		
Yan Cai et al. 2019	94	3.191	0.663 to 9.045	0.29	10.71		
Bounous et al. 2016	203	10.345	6.519 to 15.378	0.62	11.07		
Lin Qiu et al. 2013	226	7.522	4.443 to 11.771	0.69	11.10		
Hermens et al. 2020	30440	32.175	31.650 to 32.703	92.28	11.40		
Total (fixed effects)	32980	30.132	29.637 to 30.630	100.00	100.00		

EOC: Epithelial ovarian cancer; CI: Confidence interval; Sig diff: Significant difference; I^2: Data heterogeneity

the results were classified and expressed in the form of odds ratio for better understanding.

According to table 3, in the EAOC group, the most prevalent ovarian malignancy was the serousal type (2.24, I2: 89.68, $P < 0.0001$), followed by endometrioid (2.11, I2:96.72, $P < 0.0001$) and clear cell (1.62, I2:98.52, $P < 0.0001$) carcinoma.

Table 4 summarizes the incidence rate of EAOC based on the parity, menopausal status, FIGO staging, as well as 5-year survival.

In the non-EAOC group, the highest frequency of ovarian malignancy belonged to the serousal type (43.79, I2:96.88, $P < 0.0001$), followed by mixed tumor (30.13, I2:99, $P < 0.0001$) (Table 5).

Table 6 shows the incidence rate of ovarian cancer based on the parity, menopausal status, FIGO staging, and 5-year survival in the non-EAOC group.

Risk factors associated with the malignant transformation in the EAOC group

To investigate malignant transformation-related risk factors in the EAOC group compared with the non-EAOC group, we used the odds ratio.

The potential confounding factors, including age, parity, infertility, history of tubal ligation, and use of oral contraceptives, were adjusted in the majority of the studies.

Regarding the type of ovarian cancer, the clear cell and endometrioid types with an odd ratio of 4.138 and 3.058, respectively, were significantly more seen in the EAOC group compared with the non-EAOC group. Nonetheless, serousal and mixed types were the most common pathology in the non-EAOC group ($P < 0.0001$).

The overall odds ratio for the role of parity and menopausal state in the EAOC group, as risk factors, was estimated to be 2.243 (I2 = 85.61, $P < 0.0001$) for the nulliparity and 2.169 (I2 = 89.10, $P < 0.0001$) for the premenopausal state in comparison with the non-EAOC group.

As shown in table 7, FIGO stage 1 and 2 in the EAOC group was 5.703 (I2 = 83.57, $P < 0.0001$) times higher than that of the non-EAOC group. In addition, their 5-year survival rate was 1.716 ($P < 0.001$) times higher than the similar types of the non-EAOC group.

In terms of age, it was observed that patients with EAOC were younger than those with non-EAOC ($P = 0.004$, standardized mean difference (SMD) = -0.338) (CI 95%: -0.454 to -0.221). The level of Ca125 in the EAOC group were lower than that in the other group, but this difference was not statistically significant (SMD=-0.357, CI 95%=-0.492 to -0.222, $P = 0.36$) (Table 8).

Discussion

In the present systematic review and meta-analysis, comprising 20 studies, 31,667 non-EAOC patients were compared with 2,826 patients with EAOC in terms of the occurrence of different types of EOC and its relevant risk factors, such as age, parity, menopausal state, FIGO staging, 5-year survival rate, and Ca125 level. To the best of our knowledge and our literature review, this is the first systematic review and meta-analysis conducted over the last 5 years in the field of endometriosis-associated malignancy. Moreover, unlike most similar studies, which only investigate the prevalence of endometriosis-associated clear cell and endometrioid type of ovarian cancer, the present work considered all types of ovarian epithelial cancer associated with endometriosis. The method

Table 6. The incidence rate of EOCs non-associated with endometriosis based on the parity, menopausal status, FIGO staging, and also 5-years survival

Non-endometriosis related ovarian cancer	Sample size	Incidence rate (%)	95% CI	Weight (%)		I^2	Sig. diff
				Fixed	Random		
Study (nulliparous)							
Acién et al. 2015	192	18.750	13.491 to 25.000	14.71	16.71	86.72	<0.0001
Bas Esteve et al. 2019	341	18.475	14.499 to 23.009	26.07	17.83		
Muangtan et al. 2018	172	16.860	11.592 to 23.308	13.19	16.43		
Yan Cai et al. 2019	94	2.128	0.259 to 7.475	7.24	14.54		
Bounous et al. 2016	203	20.690	15.337 to 26.920	15.55	16.84		
Tong Ren et al. 2017	304	10.197	7.034 to 14.162	23.25	17.64		
Total (fixed effects)	1306	15.160	13.261 to 17.216	100.00	100.00		
Study (multiparous)							
Acién et al. 2015	192	58.854	51.541 to 65.889	14.71	16.70	95.22	<0.0001
Bas Esteve et al. 2019	341	60.411	55.001 to 65.637	26.07	17.09		
Muangtan et al. 2018	172	47.093	39.451 to 54.837	13.19	16.60		
Yan Cai et al. 2019	94	12.766	6.774 to 21.238	7.24	15.84		
Bounous et al. 2016	203	34.975	28.432 to 41.965	15.55	16.75		
Tong Ren et al. 2017	304	44.408	38.737 to 50.189	23.25	17.03		
Total (fixed effects)	1306	46.990	44.260 to 49.733	100.00	100.00		
Study (pre-menopause)							
Acién et al. 2015	192	28.125	21.888 to 35.051	6.72	10.04	96.80	<0.0001
Bas Esteve et al. 2019	341	24.340	19.879 to 29.253	11.90	10.23		
Boyraz et al. 2013	1086	44.015	41.036 to 47.026	37.82	10.40		
Muangtan et al. 2018	172	18.023	12.587 to 24.596	6.02	9.99		
Wang et al. 2013	226	31.416	25.423 to 37.904	7.90	10.10		
Lim et al. 2010	221	5.430	2.837 to 9.293	7.72	10.09		
Mangili et al. 2012	65	4.615	0.962 to 12.901	2.30	9.28		
Qianwen Li et al. 2019	128	24.219	17.087 to 32.581	4.49	9.83		
U Chul Ju et al. 2018	129	16.279	10.369 to 23.801	4.52	9.84		
Tong Ren et al. 2017	304	18.092	13.930 to 22.889	10.61	10.20		
Total (fixed effects)	2864	28.202	26.562 to 29.886	100.00	100.00		
Study (Post-menopause)							
Acién et al. 2015	192	55.729	48.401 to 62.878	5.81	8.35	96.06	<0.0001
Bas Esteve et al. 2019	341	54.252	48.801 to 59.629	10.29	8.55		
Boyraz et al. 2013	1086	47.698	44.691 to 50.717	32.71	8.72		
Muangtan et al. 2018	172	45.930	38.320 to 53.683	5.21	8.30		
Wang et al. 2013	226	53.540	46.807 to 60.179	6.83	8.42		
Lim et al. 2010	221	21.267	16.065 to 27.258	6.68	8.41		
Mangili et al. 2012	65	30.769	19.911 to 43.447	1.99	7.60		
Qianwen Li et al. 2019	128	22.656	15.729 to 30.891	3.88	8.15		
Shuang et al. 2014	210	28.095	22.127 to 34.694	6.35	8.39		
Huimin Bai et al. 2016	237	11.392	7.643 to 16.141	7.16	8.44		
U Chul Ju et al. 2018	129	29.457	21.762 to 38.122	3.91	8.15		
Tong Ren et al. 2017	304	36.513	31.091 to 42.201	9.18	8.52		
Total (fixed effects)	3311	39.937	38.267 to 41.626	100.00	100.00		
Study (FIGO stage 1,2)							
Acién et al. 2015	192	38.021	31.128 to 45.290	0.56	6.49	<0.0001	92.89
Bas Esteve et al. 2019	341	37.830	32.662 to 43.212	1.00	7.01		
Boyraz et al. 2013	1086	18.877	16.590 to 21.333	3.17	7.54		
Kumar et al. 2011	226	10.619	6.924 to 15.388	0.66	6.66		
Muangtan et al. 2018	172	19.186	13.590 to 25.875	0.50	6.36		
Wang et al. 2013	226	14.602	10.269 to 19.891	0.66	6.66		
Lim et al. 2010	221	7.692	4.545 to 12.031	0.65	6.64		
Qianwen Li et al. 2019	128	29.687	21.940 to 38.401	0.38	5.98		
Yan Cai Et al. 2019	94	9.574	4.472 to 17.399	0.28	5.52		
Bounous et al. 2016	203	13.300	8.951 to 18.759	0.59	6.55		
Huimin Bai et al. 2016	237	11.392	7.643 to 16.141	0.69	6.70		
Hermens et al .2020	30440	21.721	21.259 to 22.189	88.74	7.81		
E Sun Paik et al. 2017	224	33.929	27.755 to 40.534	0.66	6.65		
Tong Ren et al. 2017	304	20.724	16.308 to 25.720	0.89	6.92		
Jiaqi Lu et al. 2017	196	20.918	15.449 to 27.289	0.57	6.51		
Total (fixed effects)	34290	21.532	21.098 to 21.971	100.00	100.00		
Study (FIGO stage 3,4)							
Acién et al. 2015	192	41.146	34.111 to 48.459	0.56	6.25	<0.0001	98.63
Bas Esteve et al. 2019	341	41.349	36.071 to 46.779	1.00	6.34		
Boyraz et al. 2013	1086	72.836	70.085 to 75.463	3.17	6.43		
Kumar et al. 201	226	50.885	44.172 to 57.575	0.66	6.28		
Muangtan et al. 2018	172	44.767	37.194 to 52.525	0.50	6.23		

EOC: Epithelial ovarian cancer; FIGO: the International Federation of Gynecology and Obstetrics; CI: Confidence interval; Sig diff: Significant difference; I^2: Data heterogeneity

Table 6. The incidence rate of EOCs non-associated with endometriosis based on the parity, menopausal status, FIGO staging, and also 5-years survival (continued)

Non-endometriosis related ovarian cancer	Sample size	Incidence rate (%)	95% CI	Weight (%)		I^2	Sig. diff
				Fixed	Random		
Wang et al. 2013	226	70.354	63.938 to 76.227	0.66	6.28		
Lim et al. 2010	221	18.100	13.257 to 23.820	0.65	6.28		
Mangili et al. 2012	65	40.000	28.040 to 52.902	0.19	5.87		
Qianwen Li et al. 2019	128	17.187	11.096 to 24.858	0.38	6.15		
Yan Cai Et al. 2019	94	5.319	1.749 to 11.978	0.28	6.04		
Shuang et al. 2014	210	30.952	24.771 to 37.681	0.61	6.27		
Bounous et al. 2016	203	42.365	35.477 to 49.478	0.59	6.26		
Hermens et al. 2020	30440	61.800	61.252 to 62.347	88.64	6.47		
E Sun Paik et al. 2017	224	29.464	23.579 to 35.902	0.66	6.28		
Tong Ren et al. 2017	304	33.882	28.577 to 39.504	0.89	6.33		
Jiaqi Lu et al. 2017	196	19.898	14.549 to 26.182	0.57	6.25		
Total (fixed effects)	34328	60.064	59.543 to 60.582	100.00	100.00		
Study (5-year survival)							
Acién et al. 2015	172	58.000	50.249 to 65.471	12.69	10.23	95.54	<0.0001
Bas Esteve et al. 2019	305	34.400	29.079 to 40.027	22.45	10.38		
Kumar et al. 2011	184	51.000	43.540 to 58.427	13.57	10.25		
Mangili et al .2012	44	38.000	23.808 to 53.870	3.30	9.31		
Qianwen Li et al. 2019	94	34.300	24.813 to 44.807	6.97	9.95		
Yan Cai Et al. 2019	54	84.600	72.189 to 92.976	4.04	9.52		
Shuang et al. 2014	131	52.000	43.104 to 60.804	9.68	10.12		
Huimin Bai et al. 2016	132	89.900	83.447 to 94.462	9.76	10.12		
U Chul Ju et al. 2018	99	70.900	60.913 to 79.596	7.34	9.98		
Jiaqi Lu et al. 2017	138	62.400	53.759 to 70.496	10.20	10.14		
Total (fixed effects)	1353	55.092	52.406 to 57.756	100.00	100.00		

EOC: Epithelial ovarian cancer; FIGO: the International Federation of Gynecology and Obstetrics; CI: Confidence interval; Sig diff: Significant difference; I^2: Data heterogeneity

of diagnosis and differentiation in all the included studies was pathological slide examination, as a result of which, with a high homogeneity coefficient, reliable data were presented.

The results of this systematic review revealed that although the incidence of clear cell and endometrioid type in the EAOC cases was 4.138 and 3.058 times higher than that in the non-EAOC group, the most common type of ovarian endometrioid carcinoma (EC) in the endometriosis group was low-grade seruosal type, followed by endometrioid and clear cell carcinoma (CCC). Additionally, the patients who belonged to FIGO staging 1 and 2 were 5.703 times more in EAOC than non-EAOC groups, and the 5-year survival rate of EAOC was 1.7 times more than the opposite group in the same stage.

According to Heidman's study (2014), the prevalence of EOC in endometriosis patients is about 2%-17%.[42] However, the low risk of malignancy sometimes leads specialists to decide to perform surgery as the first step of the treatment, which can contribute to infertility and early menopause, the need to perform repeated surgeries and a decrease in the quality of life of the affected women. On a number of occasions, even the IVF men are hesitant to pick up these patients due to the possibility of malignancy spread to the abdominal cavity. Thus, since endometriosis is not precancerous lesion identifying the risk factors of malignant transformation in these patients paves the way of choosing the best treatment and follow-up method, especially for those in the reproductive age.

The incidence rate of EAOC in our study was about 7.34%, which is slightly higher than the 3.4% reported among women in northern Thailand in 2006, and similar to 7.5% reported in Wang's article.[38] Meanwhile, recent studies have also reported a prevalence of 11.2 to 29% for EAOC. The reason for this variability may be that certain papers have investigated only two subtypes of EC, and CCC in the field of endometriosis while others have studied all types of EOC.[43-46] Another reason is that in some studies, such as that by Shafrir et al., the self-reporting system was the basis for the diagnosis of the disease, and in the rest of the well-designed studies, the histologically proven endometriosis in EOC samples was the basis.[47]

Table 7. Comparison of frequency, risk factors and FIGO stage of endometriosis and non-endometriosis associated ovarian cancer based on odds ratio

Study (serous carcinoma)	Intervention (endometriosis)	Controls (non-endometriosis)	Odds ratio	95% CI	z	*P*	Weight (%) Fixed	Weight (%) Random	I^2	Sig. diff
Acién et al. 2015	2/20	89/172	0.104	0.0233 to 0.460			0.38	8.55	87.96	< 0.0001
Bas Esteve et al. 2019	3/36	146/305	0.0990	0.0297 to 0.330			0.58	9.93		
Boyraz et al. 2013	6/45	556/1041	0.134	0.0563 to 0.320			1.11	11.61		
Kumar et al. 2011	23/42	148/184	0.294	0.145 to 0.598			1.67	12.37		
Muangtan et al. 2018	7/31	44/141	0.643	0.258 to 1.604			1.00	11.38		
Wang et al. 2013	3/50	150/209	0.0251	0.00752 to 0.0838			0.58	9.92		
Bounous et al. 2016	17/45	82/158	0.563	0.285 to 1.109			1.82	12.50		
Lin Qiu et al. 2013	3/17	150/209	0.0843	0.0234 to 0.304			0.51	9.54		
Hermens et al. 2020	694/1979	13138/28461	0.630	0.573 to 0.693			92.36	14.18		
Total (fixed effects)	758/2265	14503/30880	0.557	0.509 to 0.610	-12.700	< 0.001	100.00	100.00		
Study (mucinous carcinoma)										
Acién et al. 2015	1/20	36/172	0.199	0.0257 to 1.536			0.45	5.41	51.96	0.0339
Bas Esteve et al. 2019	6/36	69/305	0.684	0.274 to 1.711			2.24	15.20		
Boyraz et al. 2013	4/45	182/1041	0.460	0.163 to 1.302			1.75	13.45		
Kumar et al. 2011	4/42	27/184	0.612	0.202 to 1.854			1.53	12.56		
Muangtan et al. 2018	2/31	28/141	0.278	0.0626 to 1.237			0.85	8.69		
Wang et al. 2013	0/50	17/209	0.109	0.00644 to 1.842			0.24	3.12		
Bounous et al. 2016	4/45	9/15	1.615	0.473 to 5.512			1.25	11.17		
Lin Qiu et al. 2013	0/17	17/209	0.314	0.0181 to 5.452			0.23	3.07		
Hermens et al. 2020	228/1979	2730/28461	1.227	1.063 to 1.417			91.46	27.34		
Total (fixed effects)	249/2265	3115/30880	1.102	0.961 to 1.263	1.385	0.166	100.00	100.00		
Study (clear cell carcinoma)										
Acién et al. 2015	3/20	6/172	4.882	1.119 to 21.300			0.61	4.70	88.37	< 0.0001
Bas Esteve et al. 2019	8/36	16/305	5.161	2.030 to 13.121			1.51	6.08		
Boyraz et al. 2013	17/45	66/1041	8.969	4.672 to 17.218			3.10	6.76		
Kumar et al. 2011	9/42	4/184	12.273	3.570 to 42.194			0.86	5.30		
Muangtan et al. 2018	11/31	9/141	8.067	2.972 to 21.897			1.32	5.91		
Wang et al. 2013	8/50	14/209	2.653	1.046 to 6.727			1.52	6.09		
Qianwen Li et al. 2019	18/69	38/94	0.520	0.264 to 1.024			2.87	6.71		
Yan Cai et al .2019	21/40	23/54	1.490	0.655 to 3.390			1.95	6.36		
Shuang et al. 2014	79/79	125/131	8.235	0.458 to 148.203			0.16	2.26		
Bounous et al. 2016	5/45	10/158	1.850	0.598 to 5.721			1.03	5.57		
Son,Joo-Hyuk et al. 2019	35/35	10/15	37.190	1.897 to 729.176			0.15	2.17		
Huimin Bai et al. 2016	105/132	132/132	0.0145	0.000873 to 0.240			0.17	2.35		
Lin Qiu et al. 2013	8/17	14/209	12.381	4.138 to 37.045			1.10	5.66		
Hermens et al. 2020	338/1979	849/28461	6.699	5.850 to 7.671			71.66	7.54		
U Chul Ju et al .2018	15/30	23/99	3.304	1.406 to 7.764			1.80	6.28		
E Sun Paik et al. 2017	21/41	65/183	1.906	0.963 to 3.774			2.82	6.69		
Tong Ren et al. 2017	37/124	44/235	1.846	1.114 to 3.060			5.15	7.07		
Jiaqi Lu et al. 2017	48/58	43/138	10.605	4.907 to 22.919			2.22	6.49		
Total (fixed effects)	786/2873	1491/31961	4.138	3.673 to 4.663	23.312	< 0.001	100.00	100.00		
Study (endometrioid carcinoma)										
Acién et al. 2015	5/20	23/172	2.159	0.716 to 6.509			0.77	5.84	94.34	< 0.0001
Bas Esteve et al. 2019	19/36	25/305	12.518	5.786 to 27.082			1.57	6.35		
Boyraz et al. 2013	15/45	146/1041	3.065	1.610 to 5.836			2.25	6.52		
Kumar et al. 2011	6/42	5/184	5.967	1.727 to 20.612			0.61	5.61		
Muangtan et al. 2018	8/31	24/141	1.696	0.678 to 4.240			1.11	6.14		
Wang et al. 2013	6/50	11/209	2.455	0.862 to 6.993			0.85	5.93		
Lim et al. 2010	82/82	120/139	26.701	1.590 to 448.459			0.12	3.11		
Mangili et al. 2012	21/21	39/44	5.987	0.316 to 113.526			0.11	2.96		
Qianwen Li et al. 2019	16/69	56/94	0.205	0.102 to 0.410			1.94	6.46		
Yan Cai et al. 2019	16/40	28/54	0.619	0.271 to 1.416			1.36	6.27		
Bounous et al. 2016	13/45	36/158	1.377	0.654 to 2.898			1.69	6.39		
Lin Qiu et al .2013	6/17	11/209	9.818	3.061 to 31.489			0.69	5.73		
Hermens et al .2020	533/1979	1950/28461	5.011	4.492 to 5.591			78.04	6.93		
U Chul Ju et al. 2018	15/30	36/99	1.750	0.767 to 3.992			1.37	6.28		
E Sun Paik et al. 2017	20/41	77/183	1.311	0.665 to 2.586			2.03	6.48		
Tong Ren et al. 2017	32/124	122/235	0.322	0.200 to 0.519			4.11	6.71		
Jiaqi Lu et al. 2017	9/58	28/138	0.722	0.317 to 1.643			1.38	6.28		
Total (fixed effects)	822/2730	2737/31866	3.058	2.768 to 3.377	22.038	< 0.001	100.00	100.00		
Study (mixed carcinoma)										
Acién et al. 2015	9/20	18/172	7.000	2.557 to 19.165			2.10	13.31	87.98	< 0.0001
Bas Esteve et al. 2019	0/36	49/305	0.0710	0.00429 to 1.176			0.27	7.37		
Boyraz et al. 2013	3/45	91/1041	0.746	0.227 to 2.453			1.50	12.71		
Muangtan et al. 2018	3/31	35/141	0.324	0.0929 to 1.133			1.36	12.51		
Wang et al. 2013	0/50	17/209	0.109	0.00644 to 1.842			0.27	7.31		
Yan Cai et al. 2019	3/40	3/54	1.378	0.263 to 7.216			0.78	11.07		
Bounous et al. 2016	6/45	21/158	1.004	0.379 to 2.660			2.25	13.41		
Lin Qiu et al. 2013	0/17	17/209	0.314	0.0181 to 5.452			0.26	7.24		
Hermens et al. 2020	186/1979	9794/28461	0.198	0.170 to 0.230			91.20	15.07		
Total (fixed effects)	210/2263	10045/30750	0.220	0.191 to 0.254	-20.635	< 0.001	100.00	100.00		

FIGO: The International Federation of Gynecology and Obstetrics; CI: Confidence interval; Sig diff: Significant difference; I^2: Data heterogeneity

Table 7. Comparison of frequency, risk factors and FIGO stage of endometriosis and non-endometriosis associated ovarian cancer based on odds ratio (continued)

Study (serous carcinoma)	Intervention (endometriosis)	Controls (non-endometriosis)	Odds ratio	95% CI	z	*P*	Weight (%) Fixed	Weight (%) Random	I^2	Sig. diff
Study (nulliparous)										
Acién et al. 2015	10/20	36/172	3.778	1.460 to 9.772			12.89	16.53	85.61	< 0.0001
Bas Esteve et al. 2019	18/36	63/305	3.841	1.889 to 7.811			23.12	17.91		
Muangtan et al. 2018	16/31	29/141	4.120	1.825 to 9.300			17.57	17.33		
Yan Cai et al. 2019	23/40	2/54	35.176	7.502 to 164.941			4.88	12.84		
Bounous et al. 2016	12/45	42/158	1.004	0.475 to 2.124			20.76	17.70		
Tong Ren et al. 2017	10/124	31/235	0.577	0.273 to 1.220			20.78	17.70		
Total (fixed effects)	89/296	203/1065	2.243	1.647 to 3.054	5.128	< 0.001	100.00	100.00		
Study (mulltiparous)										
Acién et al. 2015	10/20	113/172	0.522	0.206 to 1.325			8.73	14.84	79.57	0.0002
Bas Esteve et al. 2019	18/36	206/305	0.481	0.240 to 0.964			15.63	17.20		
Muangtan et al. 2018	15/31	81/141	0.694	0.318 to 1.514			12.46	16.36		
Yan Cai et al. 2019	17/40	12/54	2.587	1.055 to 6.344			9.41	15.18		
Bounous et al. 2016	33/45	71/158	3.370	1.622 to 7.002			14.16	16.84		
Tong Ren et al. 2017	59/124	135/235	0.672	0.434 to 1.041			39.62	19.58		
Total (fixed effects)	152/296	618/1065	0.925	0.709 to 1.209	-0.569	0.570	100.00	100.00		
Study (premenopause)										
Acién et al. 2015	11/20	54/172	2.671	1.045 to 6.823			5.92	9.63	89.10	< 0.0001
Bas Esteve et al. 2019	20/36	83/305	3.343	1.653 to 6.760			10.50	10.39		
Boyraz et al. 2013	21/45	478/1041	1.031	0.567 to 1.875			14.55	10.69		
Muangtan et al. 2018	11/31	31/141	1.952	0.845 to 4.506			7.44	9.97		
Wang et al. 2013	13/50	71/209	0.683	0.341 to 1.367			10.82	10.42		
Lim et al. 2010	57/82	12/139	24.130	11.331 to 51.387			9.11	10.23		
Mangili et al .2012	6/21	3/44	5.467	1.211 to 24.668			2.29	7.63		
Qianwen Li et al. 2019	11/69	31/94	0.385	0.178 to 0.836			8.67	10.17		
U Chul Ju et al. 2018	18/30	21/99	5.571	2.322 to 13.366			6.80	9.85		
Tong Ren et al. 2017	53/124	55/235	2.443	1.532 to 3.896			23.91	11.01		
Total (fixed effects)	221/508	839/2479	2.169	1.758 to 2.676	7.223	< 0.001	100.00	100.00		
Study (post-menopause)										
Acién et al. 2015	9/20	107/172	0.497	0.195 to 1.264			4.68	7.59	83.13	< 0.0001
Bas Esteve et al. 2019	16/36	185/305	0.519	0.259 to 1.041			8.41	8.59		
Boyraz et al. 2013	24/45	518/1041	1.154	0.634 to 2.099			11.41	8.98		
Muangtan et al .2018	20/31	79/141	1.427	0.636 to 3.199			6.26	8.13		
Wang et al. 2013	4/50	121/209	0.0632	0.0220 to 0.182			3.65	7.06		
Lim et al. 2010	23/82	47/139	0.763	0.420 to 1.385			11.47	8.99		
Mangili et al. 2012	15/21	20/44	3.000	0.981 to 9.170			3.27	6.82		
Qianwen Li et al. 2019	23/69	29/94	1.121	0.576 to 2.179			9.23	8.72		
Shuang et al. 2014	24/79	59/131	0.533	0.295 to 0.961			11.71	9.01		
Huimin Bai et al. 2016	32/132	27/132	1.244	0.696 to 2.224			12.10	9.05		
U Chul Ju et al. 2018	12/30	38/99	1.070	0.464 to 2.467			5.85	8.01		
Tong Ren et al. 2017	16/124	111/235	0.165	0.0923 to 0.297			11.96	9.04		
Total (fixed effects)	218/719	1341/2742	0.607	0.502 to 0.733	-5.186	< 0.001	100.00	100.00		
Study (FIGO stage 1.2)										
Acién et al. 2015	13/20	73/172	2.519	0.957 to 6.626			0.78	5.57	83.57	< 0.0001
Bas Esteve et al. 2019	29/36	129/305	5.652	2.401 to 13.305			1.00	6.09		
Boyraz et al. 2013	27/45	205/1041	6.117	3.305 to 11.322			1.93	7.26		
Kumar et al. 2011	20/42	24/184	6.061	2.885 to 12.730			1.33	6.64		
Muangtan et al. 2018	14/31	33/141	2.695	1.202 to 6.045			1.12	6.32		
Wang et al. 2013	17/50	33/209	2.747	1.374 to 5.496			1.53	6.88		
Lim et al. 2010	63/82	17/139	23.796	11.565 to 48.962			1.41	6.74		
Qianwen Li et al. 2019	31/69	38/94	1.202	0.641 to 2.253			1.86	7.20		
Yan Cai et al. 2019	26/40	9/54	9.286	3.532 to 24.413			0.78	5.58		
Bounous et al. 2016	16/45	27/158	2.677	1.280 to 5.598			1.35	6.66		
Huimin Bai et al. 2016	105/132	27/132	15.123	8.316 to 27.505			2.05	7.35		
Hermens et al. 2020	1267/1979	6612/28461	5.880	5.343 to 6.47			79.85	9.10		
E Sun Paik et al. 2017	38/41	76/183	17.833	5.309 to 59.902			0.50	4.56		
Tong Ren et al. 2017	61/124	63/235	2.643	1.677 to 4.168			3.54	8.01		
Jiaqi Lu et al. 2017	51/58	41/138	17.237	7.219 to 41.155			0.97	6.02		
Total (fixed effects)	1778/2794	7407/31646	5.703	5.239 to 6.208	40.193	< 0.001	100.00	100.00		
Study (FIGO stage 3.4)										
Acién et al. 2015	7/20	79/172	0.634	0.241 to 1.666			0.83	6.03	85.34	< 0.0001
Bas Esteve. et al 2019	6/36	141/305	0.233	0.0941 to 0.575			0.94	6.26		
Boyraz et al. 2013	18/45	791/1041	0.211	0.114 to 0.389			2.06	7.34		
Kumar et al. 2011	21/42	115/184	0.600	0.306 to 1.178			1.70	7.12		
Muangtan et al. 2018	17/31	77/141	1.009	0.462 to 2.204			1.27	6.73		
Wang et al. 2013	0/50	159/209	0.00313	0.000190 to 0.0517			0.098	1.87		
Lim et al. 2010	19/82	40/139	0.746	0.397 to 1.403			1.94	7.28		
Mangili et al. 2012	8/21	26/44	0.426	0.147 to 1.237			0.68	5.66		
Qianwen Li et al. 2019	3/69	22/94	0.149	0.0425 to 0.520			0.49	5.01		
Yan Cai et al. 2019	14/40	5/54	5.277	1.711 to 16.278			0.61	5.44		
Shuang et al. 2014	17/79	65/131	0.278	0.147 to 0.526			1.91	7.26		

FIGO: The International Federation of Gynecology and Obstetrics; CI: Confidence interval; Sig diff: Significant difference; I^2: Data heterogeneity

Table 7. Comparison of frequency, risk factors and FIGO stage of endometriosis and non-endometriosis associated ovarian cancer based on odds ratio (continued)

Study (serous carcinoma)	Intervention (endometriosis)	Controls (non-endometriosis)	Odds ratio	95% CI	z	*P*	Weight (%) Fixed	Weight (%) Random	I^2	Sig. diff
Bounous et al. 2016	29/45	86/158	1.517	0.764 to 3.013			1.64	7.08		
Hermens et al. 2020	663/1979	18812/28461	0.258	0.235 to 0.285			82.96	8.57		
E Sun Paik et al. 2017	3/41	66/183	0.140	0.0416 to 0.471			0.52	5.14		
Tong Ren et al. 2017	8/124	103/235	0.0884	0.0413 to 0.189			1.33	6.80		
Jiaqi Lu et al. 2017	7/58	39/138	0.348	0.146 to 0.834			1.02	6.38		
Total (fixed effects)	840/2762	20626/31689	0.275	0.252 to 0.300	-29.322	< 0.001	100.00	100.00		
Study (5-year survival)										
Acién et al. 2015	6/20	99/172	0.325	0.120 to 0.880			7.29	9.32		
Bas Esteve et al. 2019	11/36	104/305	0.841	0.398 to 1.775			12.92	11.42		
Kumar et al. 2011	26/42	93/184	1.568	0.789 to 3.116			15.29	11.97		
Mangili et al. 2012	9/21	16/44	1.282	0.446 to 3.682			6.48	8.85		
Qianwen li et al. 2019	23/34	32/94	4.033	1.748 to 9.305			10.32	10.64		
Yan Cai et al. 2019	34/40	45/54	1.100	0.346 to 3.492			5.41	8.12		
Shuang et al. 2014	55/79	68/131	2.174	1.204 to 3.929			20.62	12.83		
Huimin Bai et al. 2016	102/105	118/132	4.382	1.136 to 16.895			3.96	6.87		
U Chul Ju et al. 2018	24/30	70/99	1.673	0.616 to 4.542			7.23	9.29		
Jiaqi Lu et al. 2017	50/58	86/138	3.894	1.698 to 8.933			10.47	10.69		
Total (fixed effects)	340/465	731/1353	1.716	1.329 to 2.216	4.136	< 0.001	100.00	100.00		

FIGO: The International Federation of Gynecology and Obstetrics; CI: Confidence interval; Sig diff: Significant difference; I^2: Data heterogeneity

In our study, unlike most similar works, the incidence of serous adenocarcinoma followed by EC and CCC was at the top in the EAOC group, whereas serous adenocarcinoma and mixed tumor were at the top in the non-EAOC group. The effort to find out whether EOC caused by endometriosis or mounted on endometriosis have a different clinical behavior is still ongoing. Yet, according to the proposed model for the pathogenesis of EOC cancers, type I of tumors including EC, CCC, and low-grade serous adenocarcinoma with their indolent clinical behavior, usually limited to the ovary and genetically, show more stability than type II of tumors.[48] These types of tumors (type I) have a common ancestry with the lesions such as endometriosis and borderline tumors and often carry K-ras and PTEN mutations.[49]Although in recent studies, endometriosis has been strongly associated with the presence of EC and CCC, considering that these two histological subtypes constitute a very small percentage of all ovarian malignancies, these are entities difficult to study and fully characterize.[7, 50, 51] However, this difference among the reports on the prevalence of tumor types in EAOC is sometimes due to the group in which mixed tumors are included because they are most commonly associated with endometriosis.[28, 52] Therefore, it is not far from expectation that in our study, with a large number of cases, all sorts of type I tumors had a higher prevalence in the EAOC group; notably, the prevalence of CCC and EC tumors was 4.138 and 3.058 times higher than that in the non-EAOC group, respectively.

As mentioned above, these EAOC tumors are classified as a type I of tumor; thus, at the time of diagnosis, they have a lower FIGO staging and consequently, a higher survival rate. These EAOC cases are usually younger and in pre-menopausal state and have lower parity than non-EAOC ones.[28, 52, 53] In our study, the average age of the EAOC participants was lower than those in the non-EAOC group (49.50 years (34.40-59.00) versus 53.62 (49.48-57.75)), most of whom were in the premenopausal state and were 7.5 times more in stages 1 and 2 of FIGO classification. Their 5-year survival rate was also 1.7 times higher than that of the non-EAOC group. Despite the difference concerning the survival rate between these two groups being still unclear, some researchers have given the following reasons to justify this difference between the two groups (type I and II of tumors).

EAOC patients often present with specific clinical symptoms, such as dysmenorrhea and dyspareunia, and in the course of their treatment, they are frequently subjected to pelvic exam and ultrasound. Furthermore, they are oriented to their condition, and all these endomerriotic patients enable faster diagnosis of malignancy at a lower FIGO stage. Nonetheless, this hypothesis is not

Table 8. Comparison of age, and Ca-125 level of endometriosis and non-endometriosis associated ovarian cancer based on odds ratio

Study (age)	N1	N2	Total	SMD	SE	95% CI	t	*P*	Weight (%)		I^2	Sig. diff
									Fixed	Random		
Acién et al. 2015	20	172	192	-0.498	0.237	-0.965 to -0.0310			6.33	8.40	62.13	0.004
Bas Esteve et al. 2019	36	305	341	-0.397	0.176	-0.745 to -0.0503			11.39	10.72		
Muangtan et al. 2018	31	141	172	-0.0858	0.198	-0.476 to 0.304			9.09	9.86		
Wang et al. 2013	50	209	259	-0.565	0.159	-0.878 to -0.252			14.05	11.48		
Mangili et al. 2012	21	44	65	-0.607	0.267	-1.141 to -0.0722			4.96	7.40		
Qianwen li et al. 2019	69	94	163	-0.633	0.162	-0.953 to -0.314			13.58	11.36		
Yan Cai et al. 2019	40	54	94	0.429	0.209	0.0138 to 0.845			8.10	9.40		
Bounous et al. 2016	45	158	203	-0.130	0.168	-0.462 to 0.202			12.50	11.07		
U Chul Ju et al. 2018	30	99	129	-0.326	0.208	-0.738 to 0.0855			8.19	9.45		
E Sun Paik et al. 2017	41	183	224	-0.417	0.173	-0.759 to -0.0759			11.81	10.86		
Total (fixed effects)	383	1459	1842	-0.338	0.0596	-0.454 to -0.221			-5.667	< 0.001	100.00	100.00
Study (Ca125)												
Acién et al. 2015	20	172	192	-0.201	0.236	-0.665 to 0.264			8.52	8.94	18.83	0.3613
Bas Esteve et al. 2019	36	305	341	-0.320	0.176	-0.667 to 0.0265			15.22	15.29		
Muangtan et al. 2018	31	141	172	-0.127	0.198	-0.517 to 0.263			12.11	12.41		
Wang et al. 2013	50	209	259	-0.557	0.159	-0.870 to -0.244			18.74	18.42		
Mangili et al. 2012	21	44	65	-0.0983	0.262	-0.622 to 0.426			6.88	7.29		
Shuang et al. 2014	79	131	210	-0.551	0.144	-0.836 to -0.267			22.66	21.76		
E Sun Paik et al. 2017	41	183	224	-0.252	0.173	-0.592 to 0.0886			15.87	15.88		
Total (fixed effects)	278	1185	1463	-0.357	0.0688	-0.492 to -0.222			-5.193	< 0.001	100.00	100.00

N1: Endometriosis related epithelial ovarian cancer; N2: Non- endometriosis related epithelial ovarian cancer; SMD: Standardized mean difference; SE: Standard error; t: Test statistic; FIGO: The International Federation of Gynecology and Obstetrics; CI: Confidence interval; Sig diff: Significant difference; I^2: Data heterogeneity

acceptable based on the study by Ren (2017),[40] since, in this study, the clinical symptoms were not different between the two groups and only the blotting was more frequently seen in the non-EAOC group. Accordingly, it is more likely to be due to the intrinsic mechanism of the disease than its different nature that led to early detection of EAOC.[38, 52] Moreover, according to Paik's (2018), endometriosis was not identified as a significant prognostic factor in tumor staging and survival rate, and after score matching propensity, there was no significant difference concerning the survival rate between these two groups of patients.[39]

Another reason behind the better prognosis of endometriosis patients is their immune status, being more active than that of the normal population. Since the proliferation of endometriosis lesions leads to more inflammatory response and the presence of tumor infiltrative T cells is associated with a better survival rate in ovarian tumors, the active immune system in these patients can play an important role in improving the prognosis of ovarian cancer.[53, 54-7]

All the medical treatments suppressing endometriosis lesions, such as oral contraceptives, progesterone, and aromatase inhibitors, according to previous studies, can reduce the risk of ovarian cancer and higher survival rate in EAOC patients.[57-60] Notably, in the advanced stages of ovarian cancer, due to the rapid growth and extensive necrosis of the mass with the loss of the malignant transformation points, endometriosis background may be removed from the adnexal mass or not necessarily included in the pathology slides.[30]

Finally, cancer lesions formation on endometriosis can be an independent entity with a separate pathophysiology, and these EAOC patients even respond to their treatment differently from other non-EAOC ones, which necessitates further investigation in this field.[61]

The transition of endometriosis to malignancy occurs in connection with an intermediated stage of atypical endometrioma, with a prevalence of about 2 to 3% between endometrioma in the premenopausal state.[62, 63] Meanwhile, in endometrioma cysts, distinguishing between the cytological and structural atypia and benign reactive atypia in connection with the underlying inflammation was highly challenging. The diagnostic criteria for pathological and clinical diagnosis of these lesions (atypia) are also still controversial.[64-7] Based on some studies, in the context of local inflammation caused by endometrioma and estrogen production, as a mitotic factor with overexpression of COX2 and aromatase enzyme activation, local production of PGE2 and local estradiol along with P53 mutation, EAOC is formed such as positive

receptor EC and negative receptor CCC. These pathways can be associated with changes in the appearance of endometriomas. Thus, in case of finding lesions larger than 10 centimeters with moderate to intense color flow or the presence of solid part with 0 to 3 papillary projections or multi-septated lesions with solid part in the ultrasound examination of these patients (Ovarian-Adnexal Reporting and Data System Ultrasound (ORADS 4, 5)), further examination of the tumor with magnetic resonance imaging or surgery seems necessary.[68] Loss of classic endometriosis T2 shading, nodular septation and restricted diffusion of the solid component of endometrioma in magnetic resonance imaging can be a sign of malignancy and necessitate surgical intervention. However, Orezzoli et al. reported in their study that the presence of clear cell in the context of endometriosis is not necessarily associated with abnormal features of endometrioma.[69]

In most patients diagnosed with endometriosis, the level of Ca125 increases slightly, and as seen in the results of the present systematic review and similar studies, the level of Ca125 in the EAOC (474.97 ± 471.31 U/ML) and non-EAOC (959.12 ± 581.63 U/ML) groups does not differ much because they are all from the EOC group ($P = 0.36$).[31] On the contrary to our study, Li and Wang reported that patients with EAOC had significantly lower Ca125 levels than those with non-EAOC.[28, 38, 70] It seems as if the high levels of Ca125, over 200 U/Ml, or a rapid increase in this factor in the follow-up period of endometriotic patients can create the possibility of malignancy in mind. Along with Ca125, measurement of human epididymis protein 4 (HE4) is done today to screen the ovarian epithelial tumors, showingno significant difference between EAOC and non-EAOC groups in the study by Qian wen li (2019).[71]

The present study indicated that EAOC occurs in younger and premenopausal women, with early FIGO stage and a higher 5-year survival rate in proportion to non-EAOC, and includes all types of type 1 of tumors (low-grade serous, CCC and EC). Meanwhile, Ca125 level was not much different between these two groups. Therefore, even though the existence of histological endometriosis is an independent beneficial prognostic factor in EOCs, to determine whether the endometriotic patient could benefit from surgery or expectant management, it is necessary to make an individual decision based on the criteria of ultrasound examination, level of Ca125 and risk factors of the patient during the follow-up. It should be noted that there is no evidence claiming that endometriosis surgery can reduce the risk of EAOC. One limitation of this study was that genetic factors, diet, smoking, hormone therapy, and poly cystic ovarian syndrome in the cancer incidence in both groups were not analyzed, and simultaneous examination of endometrial cancer was not conducted. Additionally, in advanced cancer stages, endometriosis may not be evident. Hence, conducting multicenter prospective studies on women with endometriosis and their long-term follow-up for ovarian cancer occurrence is recommended.

Conclusion

The risk of malignancy of endometriosis ovarian lesions was found to be directly correlated with age, nulliparity and menopausal status. Even though endometriosis-associated malignancies are slow-growing and often limited to the ovaries at the time of diagnosis, and that they have a good 5-year survival rate, there is no specific marker to identify them. Given the global prevalence of endometriosis, it seems that paying further attention to patients' symptoms, along with timely diagnosis and efficient follow-up of endometriosis patients, as well as complete surgery at the end of the reproductive years could prevent unwanted complications and disease progression to malignancy. These measures might also reduce the financial and psychological burden on society and patients.

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Data Availability Statement

The datasets used and/or analyzed during the

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Authors' Contribution

EA: Conception and design, data collection, drafting and reviewing the manuscript; KC: Conception and design, data collection, drafting and reviewing the manuscript; AMKH: Conception and design, data collection, drafting and reviewing the manuscript, data analysis and interpretation, statistical analysis. SA: Conception and design, data collection, drafting and reviewing the manuscript; All authors read and approved the final and agree with all parts of the work in ensuring that any queries about the accuracy or integrity of any component of the work are appropriately investigated and handled.

Conflict of Interest

None declared.

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