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REVIEW

Hysterectomy and risk of ovarian cancer: a systematic review and meta-analysis

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Abstract

Purpose The association between hysterectomy for benign gynecologic disease and ovarian cancer risk was controversial. Thus, we perform a systematic review and meta-analysis to evaluate the effect of hysterectomy and ovarian cancer risk.

Methods PubMed, Cochrane Library, and Embase were searched from 2000 toJanuary 2018. A random-effect model was used to obtain the summary odds risks (ORs) and 95% confidence intervals (CIs).

Results A total of 18 case–control studies were included in the meta-analysis. We found that there was no statistical significance for ovarian cancer risk following hysterectomy (OR 0.97, 95% CI 0.83–1.12). And in subgroup analysis, the protective effects were observed for invasive endometrioid/clear cell carcinomas after hysterectomy (OR 0.70, 95% CI 0.51, 0.94; $I^2 = 0\%$), and no statistical significance for serous and mucinous.

Conclusions Hysterectomy showed no relationship with ovarian cancer. But a reduced risk was found for endometrioid-invasive OC. These findings could provide evidence for patients with benign gynecological disease and clinicians to make appropriate decision about whether to conduct hysterectomy.

Keywords Hysterectomy · Ovarian cancer · Risk · Meta-analysis

Introduction

Hysterectomy as one of the most common gynecological procedures is always performed for benign gynecologic conditions [1, 2]. However, uterus preservation in benign gynecologic disease is preferred by patients in most time because it could improve the quality of life [3]. The two measures have their own risks and benefits; so, it is complex yet whether women should be advised to have their uterus removed or conserved for benign gynecological disease [4–7], and the final decision may be based on additional effects, such as cancer risk.

The results from observational studies about whether hysterectomy reduced ovarian cancer (OC) risk were controversial. Some studies showed that hysterectomy might reduce the OC risk [8, 9]. However, several recent studies suggested positive or null association between hysterectomy and OC risk [10–12]. Additionally, the previous meta-analyzes did not get consistent results because of the different number of included studies and insufficient statistical power [13–15].

Clinical guidelines about hysterectomy for benign disease as one of the preventions for ovarian cancer also were

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inconsistent [16–18]. Given the inadequate evidence about this topic, we, therefore, perform a systematic review and meta-analysis to evaluate the effect of hysterectomy and ovarian cancer risk, and conduct subgroups to determine whether risk varies by the histological types of OC, study participant source, and several important confounding factors.

Materials and methods

Literature search

PubMed, Cochrane Library, and Embase were searched from 2000 to January 2018; we identified studies using keywords including variations on "hysterectomy" AND "ovarian cancer". We also searched the reference lists of relevant articles to identify potentially eligible studies. Searches were limited to English studies and conducted in humans.

Selection criteria

Two authors independently evaluated the eligibility to determine whether they met all of the inclusion criteria. Disagreements were resolved by discussion or consultation with third author. The inclusion criteria for studies included the following:(1) a case–control study, or nested case–control study; (2) included patients who were histologically diagnosed ovarian cancer; (3) evaluated the association between hysterectomy for benign disease and ovarian cancer risk, which was then compared with women who never received hysterectomy; (4) the outcome measured was ovarian cancer incidence, measured as an odds ratio (OR) ora relative risks (RR), as estimated with 95% confidence intervals (CIs) (or with sufficient data for calculating them). When the publications were from the same oroverlapping data, we selected the most recent or largest population. The exclusion criteria were as follows: (1) the participants were high-risk population (e.g., women with BRCA1/2 mutations); (2) the outcome was specific histological types of OC; (3) review articles, case report, editorial comments, expert opinion and letters.

Data extraction

Data extracted from the included studies were the name of the first author, year of publication, country, interventions, the main outcome, available subgroups, effect estimates with corresponding 95% confidence intervals (CIs) and variables controlled for in multivariable models. Two independent reviewers extracted data from eligible studies, and a third reviewer was consulted for resolution of disagreements.

Quality assessment

We evaluated the quality of eligible studies using the Newcastle–Ottawa scale (NOS) for the assessment of case–control studies [19]. The NOS includes three parts: selection, comparability and exposure. The quality scores of studies ranged from zero to nine, with seven–nine points indicating a high-quality study and zero–six points indicating low quality. All papers scores are higher than 6 stars, so these papers are included. The quality of the included studies was independently appraised by two reviewers, and disagreements were resolved by a third reviewer.

Statistical analysis

The meta-analysis was conducted using STATA software package (version 12.0, Stata Corp LP). We used the odds ratios (OR) with 95% CI as measures of the association strength. A random-effect model was used in data analysis procedure. And the heterogeneity between studies was evaluated by I^2 test. And we prespecified subgroup analyzes according to the histological types of OC, study participant source. We also stratified the meta-analysis by potentially important confounding factors, including parity, family history of ovarian cancer, oral contraceptive use and race. To evaluate the influence of single studies on the overall estimate, sensitivity analysis was performed. Publication bias was evaluated via the Egger linear regression test [20].

Results

Study identification and selection

A flow diagram of the study selection is shown in Fig. 1. A total of 5309 studies were identified in the literature search, and then excluded 5257 studies by Endnote X8 software finding duplicates and nonrelevant studies (based on title and abstracts). 6 additional records were identified from reference lists manually. 58 articles were then examined, and 40 were excluded, the reasons for which are shown in Fig. 1. Finally, 18 studies [11, 12, 21–36] were included in the meta-analysis.

Study characteristics

Table 1 summarizes the characteristics of the meta-analyzed studies. We abstracted 19 estimates from 18 studies, because one of the studies divided into White women and African–American women [27]. Overall, all studies

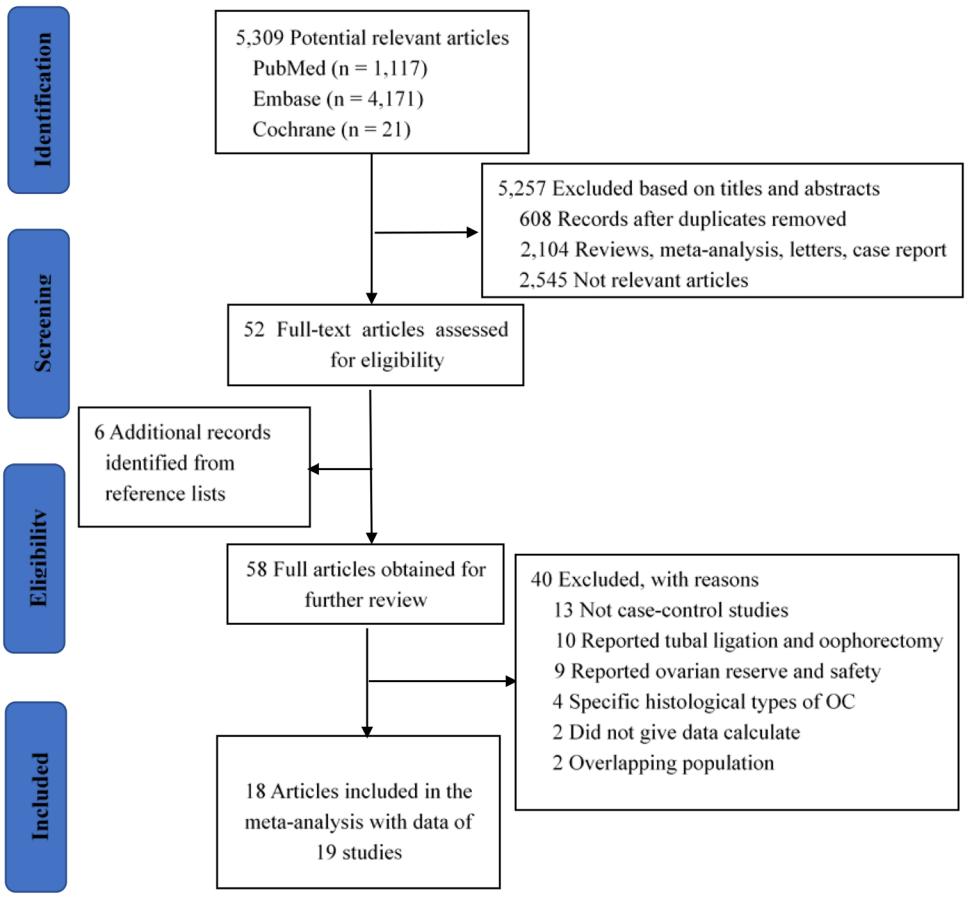

Fig 1 Flow chart of study selection in the current meta-analysis

included seventeen case–control studies and one nested case–control study [21].

The included studies were published between 2000 and 2017, and they yielded a total of 14,440 OC cases. These studies were conducted in different geographic locations; particularly, 12 of them were conducted in the United States [11, 12, 21, 22, 24, 25, 27, 28, 30, 33–35], 4 in Europe [26, 29, 31, 36], 1 in China [32], 1 in Asian [23]. In aspect of study setting, 13 of these studies were population based, 5 of them were hospital based [11, 26, 31, 32, 35]. Of these studies, 3 investigated the association between hysterectomy alone with ovarian cancer risk [23, 26, 33] and others were not clear about hysterectomy definition, we could not identify whether the hysterectomy with salpingectomy or unilateral salpingo-oophorectomy. All studies were adjusted for age, and most studies were adjusted for potential confounders, including parity, oral contraceptive use, breastfeeding, body mass index (BMI), and race.

Meta-analysis

Of the 18 selected studies with data of 19 studies, 3 of them found that hysterectomy significantly reduced the risk of OC, 2 studies showed that hysterectomy increased ovarian cancer risk, the other 14 studies found null association between ovarian cancer risk and hysterectomy. In our meta-analysis, there was no statistical significance for ovarian cancer risk following hysterectomy (OR 0.97, 95% CI 0.83–1.12), with high between-study heterogeneity ($I^2 = 73.0\%$, $P < 0.001$) (Fig. 2).

Subgroup analysis

Subgroup analyzes were conducted to explore the possible sources of heterogeneity. Results of subgroup meta-analyzes are summarized in Table 2. In the analysis stratified by tumor histologic type, we observed that there was no statistical significance for both invasive tumor and borderline tumor (OR 0.81, 95% CI 0.65, 1.01 vs OR 0.96, 95% CI 0.54, 1.71) (Fig. 3). Additionally, the risks reduction was found for invasive endometrioid/clear cell carcinomas after hysterectomy (OR 0.70, 95% CI 0.51, 0.94; $I^2 = 0\%$), and no statistical significance for serous invasive (OR 0.98, 95% CI 0.76, 1.25; $I^2 = 22.7\%$) and mucinous invasive (OR 0.73, 95% CI 0.40, 1.35; $I^2 = 0\%$) (Fig. 4).

In addition, there was no statistical significance in both population-based (OR 0.97, 95% CI 0.85, 1.11; $I^2 = 63.7\%$) and hospital-based case–control studies (OR 0.99, 95% CI

Table 1 Characteristics of 18 case-control studies included in a meta-analysis examining the association between hysterectomy and ovarian cancer risk

References	Country	Intervention	Outcome	Available subgroups	Cases	Controls	Total sample size	OR	95% CI
Kupelian et al. [35][A]	USA	Hysterectomy	OC	None	348	494	842	0.90	0.60–1.50
Beard et al. [21]	Olmsted	Hysterectomy	Invasive EOC	None	129	129	258	0.50	0.20–0.96
Modugno et al. [22]	Delaware Valley	Hysterectomy	EOC	Histologic type	767	1367	2134	0.73	0.55–1.02
Riman et al. [36]	Sweden	Hysterectomy	Invasive EOC	Histologic type	655	3899	4554	0.71	0.47–1.06
Rutter et al. [23]	Israeli	Hysterectomy alone	EOC	None	598	2396	2994	0.69	0.50–0.95
Mills et al. [24]	CentralCalifornia	Hysterectomy	EOC	Histologic type	256	1522	1778	1.14	0.80–1.64
Modugno et al. [25]	US	Hysterectomy	EOC	None	2098	2953	5051	0.99	0.83–1.18
Chiaffarino et al. [26][A]	Multistate, Italian	Hysterectomy alone	Invasive EOC	None	1031	2411	3442	0.60	0.40–0.90
Moorman et al. [27]	North Carolina	Hysterectomy	EOC	None	943	868	1811	1.22	0.97–1.54
Moorman et al. [27]	North Carolina	Hysterectomy	EOC	None	143	189	332	1.07	0.61–1.87
Ness et al. [28]	US	Hysterectomy	EOC	None	869	1778	2647	1.24	0.99–1.53
Faber et al. [29]	Denmark	Hysterectomy	EOC	None	554	1564	2118	1.55	1.15–2.08
Rice et al. [33]	New England	Hysterectomy alone	EOC	Histologic type	2265	2333	4598	1.09	0.83–1.42
Pajenga et al. [31][A]	Albania	Hysterectomy	OC	None	283	1019	1302	0.59	0.41–1.39
Pasalich et al. [32][A]	Southern China	Hysterectomy	OC	None	500	500	1000	0.86	0.46–1.62
Merritt et al. [30]	USA	Hysterectomy	Invasive OC	Histologic type	1571	2100	3671	1.04	0.81–1.33
Le et al. [12]	British Columbia	Hysterectomy	EOC	None	608	335	943	0.83	0.60–1.16
Ruiz et al. [11][A]	Kansas	Hysterectomy	EOC	None	208	224	432	3.60	2.10–6.20
Peres et al. [10]	Multistate African–American	Hysterectomy	EOC	None	614	743	1357	0.75	0.56–1.01

OR odds ratio, *CI* confidence interval, *OC* ovarian cancer, *EOC* epithelial ovarian cancer

[a]White women

[b]African–American women

[c]Estimate calculated by pooling estimates presented for women with type I and type II ovarian cancers

[A]Hospital-based population

0.52, 1.89; $I^2 = 87.0\%$). Additionally, we found hysterectomy alone show no relationship with ovarian cancer risk (OR 0.78, 95% CI 0.54, 1.13; $I^2 = 74.0\%$), also hysterectomy which definition was not clear (OR 1.01, 95% CI 0.86, 1.19; $I^2 = 72.4\%$). Additionally, we found that hysterectomy was associated with a reduced risk of ovarian cancer, if the study was adjusted for oral contraceptive use (OR 0.87, 95% CI 0.77, 0.99; $I^2 = 41.4\%$). But there was no association between hysterectomy and ovarian cancer risk regardless of weather the studies adjusted for parity, family history of OC or race (Table 2).

Sensitivity analysis and publication bias

To assess the stability of pooled result in our meta-analysis, we performed a sensitivity analysis by sequential omission of the individual study. The pooled ORs and 95% CI were not significantly changed, which suggested the robustness of the results. Publication bias was evaluated via Egger's test. The Egger's test ($P > 0.05$) suggested no significant publication bias.

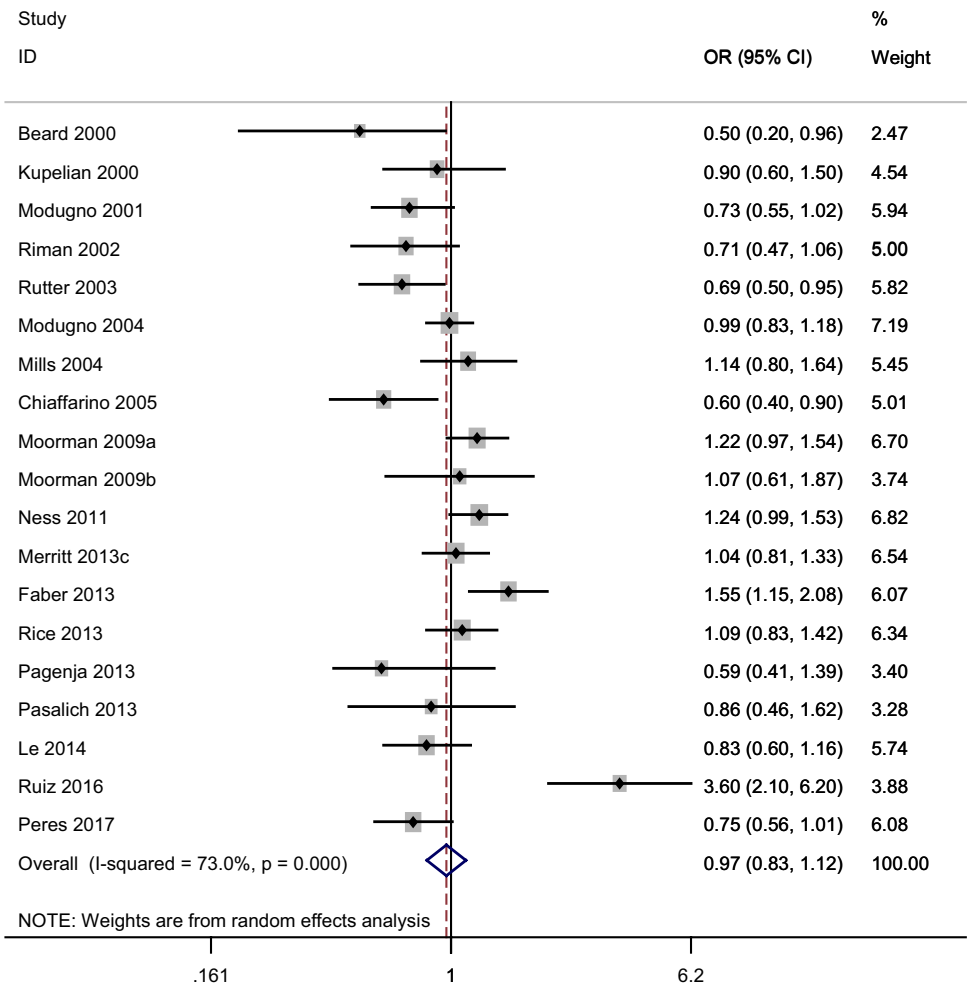

Fig 2 Forest plot for 18 studies for the association between hysterectomy and ovarian cancer risk. Studies are ordered by publication years. The black boxes show the effect estimate for individual studies and the size of the gray boxes represents the weight of individual studies in the summary estimate

Discussion

This systematic review and meta-analysis suggested that hysterectomy showed no relationship with ovarian cancer. But a reduced risk was found for endometrioid-invasive OC. These findings could provide evidence for patients with benign gynecological disease and clinicians to make appropriate decision about whether to conduct hysterectomy.

Our results showed that hysterectomy had no relationship with ovarian cancer risk; this was consistent with a recent meta-analysis, but different with the two old meta-analyzes. In 2013, a meta-analysis by Jordan et al. [14] showed that there has been a temporal shift in the association between hysterectomy and ovarian cancer incidence. Their main explanation was the use of estrogen-only hormone replacement therapy (HRT) in hysterectomized women. Recently, Peres et al. [34] showed that there was a positive association for premenopausal hysterectomy and OC risk only among women using estrogen therapy, and the protective effect was found in hysterectomized women who never used hormone therapy. Therefore, the potential mechanism may really be changes in hormone therapy recommendations and patterns of hormone therapy use over time. But the exact association of the positive effect has not yet been fully elucidated, and further studies are needed, which must include hormone therapy regimens and duration, also dose effect.

In subgroup analyzes, we found that ovarian cancer incidence had no difference in hysterectomy alone and hysterectomy, the latter's definitions were not mentioned in the studies, which might be hysterectomy alone, hysterectomy with unilateral or bilateral salpingectomy, and hysterectomy with unilateral or bilateral oophorectomy. There have been a growing number of arguments demonstrating the high-grade pelvic serous carcinomas, which might originate from fallopian tube [37]. Therefore, based on this theory,some guidelines and clinicians might recommend salpingectomy at the time of hysterectomy or other pelvic surgery to prevent ovarian cancer. But our results showed no difference in hysterectomy alone and hysterectomy (the definition was not clear), which was inconsistent with some studies probably due to bias. So, additional well-designed randomized prospective trial is needed to fully understand ovarian cancer risk following hysterectomy or opportunistic salpingectomy.

Table 2 Results of subgroup meta-analyze`

Subgroups	Number of studies	OR (95% CI)	I^2 (%)	*P*-heterogeneity
Tumor type				
Invasive	6	0.81 (0.65, 1.01)	48.3	0.085
Borderline	2	0.96 (0.54, 1.71)	29.1	0.235
Histology of invasive OC				
Serous	4	0.98 (0.76, 1.25)	22.7	0.274
Mucinous	4	0.73 (0.40, 1.35)	0.0	0.511
Endometrioid	4	0.70 (0.51, 0.94)	0.0	0.474
Study participant source				
Population-based	14	0.97 (0.85, 1.11)	63.7	0.001
Hospital-based	5	0.99 (0.52, 1.89)	87.0	< 0.001
Hysterectomy definition				
Hysterectomy alone	3	0.78 (0.54, 1.13)	74.0	0.021
Not clear about hysterectomy definition	16	1.01 (0.86, 1.19)	72.4	< 0.001
Adjustment for OCU				
Not adjusted	8	1.16 (0.87, 1.54)	79.2	< 0.001
Adjusted	11	0.87 (0.77, 0.99)	41.4	0.073
Adjustment for parity				
Not adjusted	12	0.92 (0.76, 1.12)	77.6	< 0.001
Adjusted	7	1.07 (0.86, 1.32)	54.9	0.039
Adjustment for family history of OC				
Not adjusted	10	1.06 (0.81, 1.38)	79.6	< 0.001
Adjusted	9	0.90 (0.77, 1.06)	60.2	0.010
Adjustment for race				
Not adjusted	13	0.89 (0.75, 1.06)	65.2	0.001
Adjusted	6	1.16 (0.85, 1.56)	83.1	< 0.001

OR odds ratio, *CI* confidence interval, *OC* ovarian cancer, *OCU* oral contraceptive use

Nevertheless, our results have shown that hysterectomy reduced invasive endometrioid/clear OC risk, and there was no statistical significance for serous and mucinous carcinomas. Consistent with our findings, a case–control study included in our analysis and a recent analysis among 1.3 million women from 21 prospective cohort studies also suggested that hysterectomy reduced the endometrioid and clear cell carcinomas [30, 38], and some other studies had different results [8, 36]. Furthermore, histopathologic studies suggested that endometrioid and clear cell carcinomas possibly resulted from endometrial cells and endometriosis lesions [39, 40]. Nevertheless, a pooled analysis of 13 case–control studies and a New England-based case–control (NECC) study also showed that endometriosis increased the risk of endometrioid and clear cell tumors [5, 33]. Therefore, a hypothesis suggests a role for retrograde transportation of carcinogens from uterus to the tubes and ovaries, which may explain that hysterectomy protects endometrioid and clear cell carcinomas by blocking endometriosis from retrograde menstruation and endometrioid cell. Similarly, many findings indicated that tubal ligation could reduce the ovarian cancer risk, especially endometrioid and serous carcinomas. The hypothesis included that not only the fallopian tube might be at the origin of most high-grade ovarian and peritoneal serous carcinomas [42], but also the retrograde menstruation theory.

Moreover, the included studies in this meta-analysis described OC histological subtypes, which analyzed the combination of endometrioid and clear cell subtypes due to the small number of clear cell cases, the close histogenetic relationship between the two subtypes and the probability of a shared pathogenesis; so, our results showed that hysterectomy not only reduced endometrioid ovarian cancer risk, but also included clear cell carcinomas.

Our meta-analysis showed some strengths. Firstly, we conducted a systematic and rigorous approach for the identification of case–control studies investigating the association of hysterectomy and OC risk. Secondly, we conducted preplanned subgroup analyzes to explore differences in histological types of OC, adjustment for parity, family history of ovarian cancer, oral contraceptive use and race to minimize bias. Thirdly, eighteen studies with a relatively large

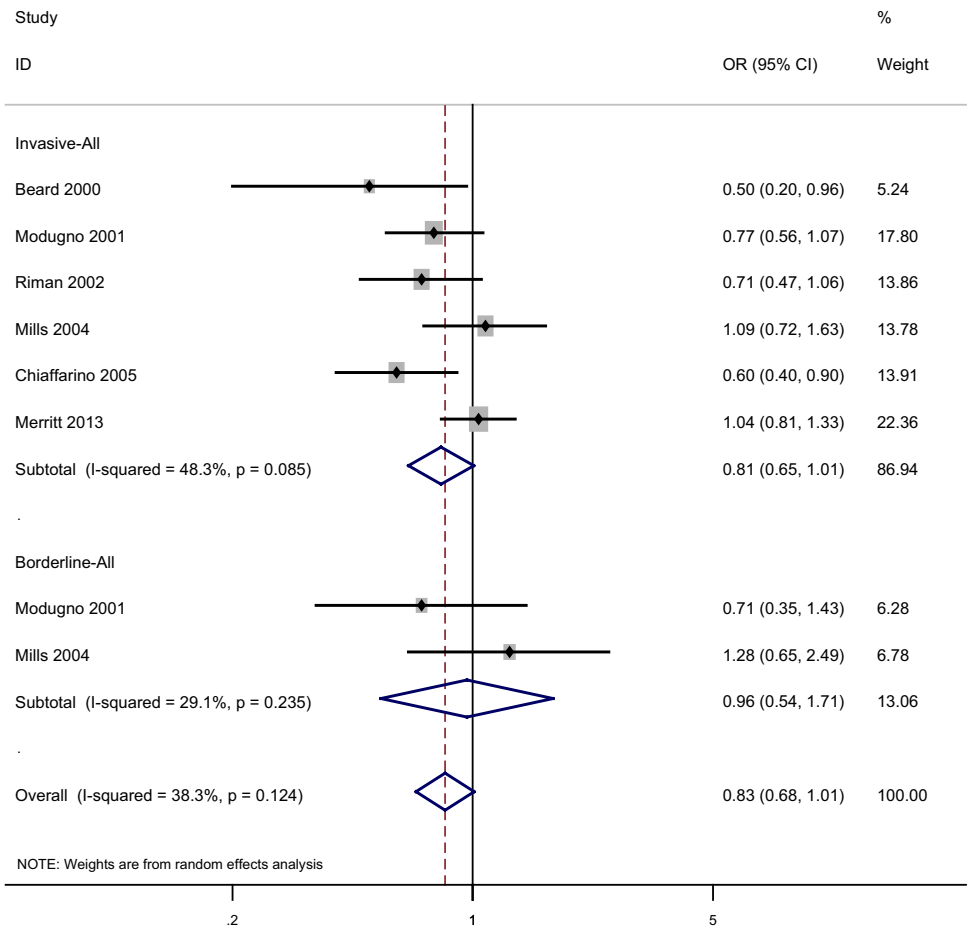

Fig 3 Forest plot for ovarian cancer risk after hysterectomy and subgroup analysis by tumor type

population were finally included, which provided sufficient statistical power to evaluate the effect of hysterectomy and OC risk. In spite of strengths, our analysis has several limitations needed to be considered. Firstly, the included studies in our meta-analysis were retrospective trials; therefore, the inherent pitfall of the present meta-analysis is important because low-quality articles and limited data might pose a certain bias [43, 44]. Secondly, we did not assess the indications for hysterectomy because of limited studies, which may confound this association. Thirdly, the adjusted confounding factors differed between studies, and we found that hysterectomy was associated with a reduced risk of ovarian cancer if the study was adjusted for oral contraceptive use, but the type and duration of contraceptive pills were not clear. Also, the included studies did not test the BRCA mutations; so we did not know if the patients mutated, and so all these factors might influence the effects of hysterectomy and OC risk.

Conclusion

Our meta-analysis showed that there was no association in the incidence of ovarian cancer following hysterectomy, but with a greater protective effect on endometrioid invasive cancers. Future studies should consider the effects of indications for hysterectomy, years since hysterectomy, age at the procedures, surgical characteristics and hormone therapy on this association. Although this study has some limitations, the results could provide evidence for patients with benign gynecological disease and clinicians to make appropriate decision about whether conduct hysterectomy.

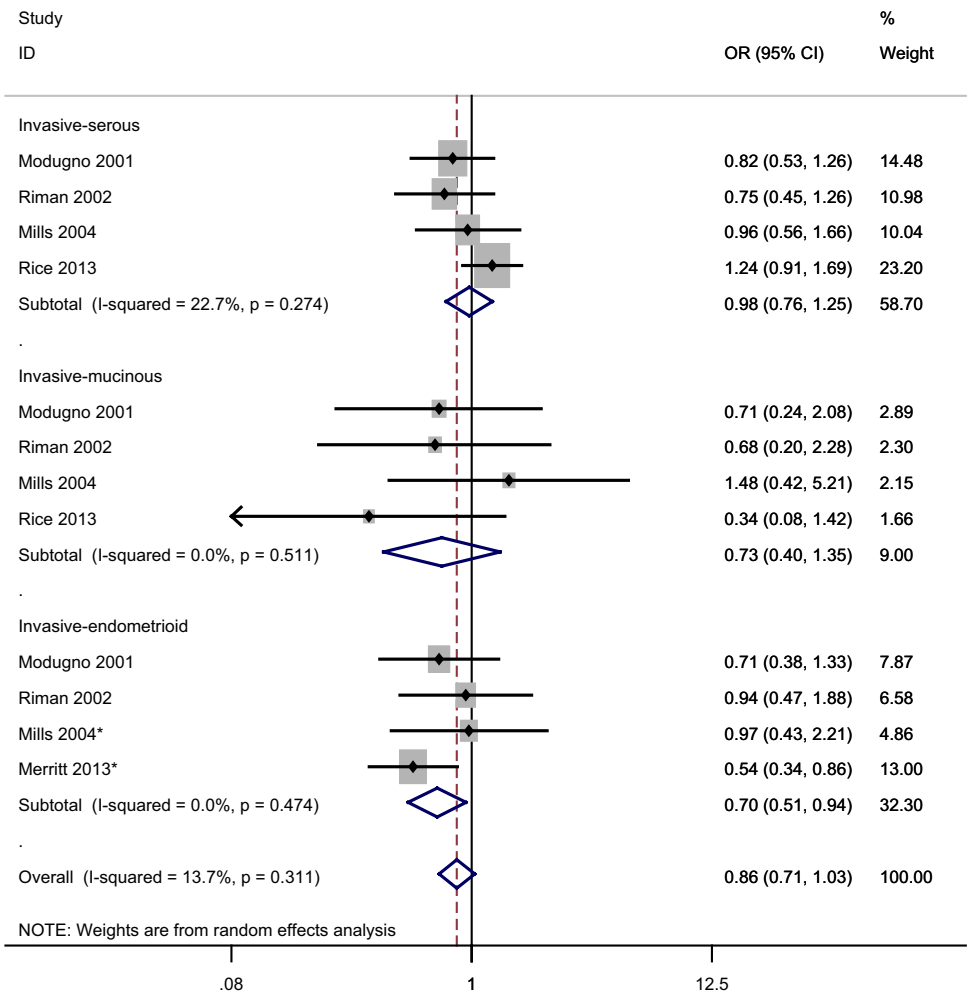

Fig 4 Forest plot for ovarian cancer risk after hysterectomy and subgroup analysis by histology of invasive ovarian cancer. Asterisk indicates estimate for endometrioid/clear ovarian cancer

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Author contributions XH and LY: Project development, data collection, manuscript writing/editing. XH and WL: Project development, data analysis, manuscript editing. JL, LZ and YG: Project development. KY and HL: Project development, manuscript editing.

Compliance with ethical standards

Conflict of interest No conflict of interest.

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