

Original Article



Prophylactic salpingectomy as a preventative strategy for ovarian cancer in the general population: a systematic review and meta-analysis

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ABSTRACT

Objective: The impact of prophylactic salpingectomy on the prevention of epithelial ovarian cancer (EOC) remains unclear, particularly in Asian populations where data is lacking. In this systematic review and meta-analysis study, we sought to assess whether prophylactic salpingectomy could reduce the incidence of ovarian cancer in the general population of multiple ethnicities.

Methods: A systematic review and meta-analysis were conducted using PubMed/MEDLINE, EMBASE, the Cochrane Library, and Web of Science to assess the effectiveness of salpingectomy, bilateral salpingectomy (BS), and unilateral salpingectomy (US) in reducing the risk of EOC and evaluating postoperative outcomes.

Results: The final analyses included 6 eligible trials (5,747,056 patients), including 1 cohort study and 5 case-control studies. The analyses of these studies demonstrated that women who underwent salpingectomy had a significantly reduced risk of EOC compared to those who did not receive salpingectomy (odds ratio [OR]=0.63; 95% confidence interval [CI]=0.45–0.89; p=0.007). Five studies (5,746,469 patients) indicated a significant reduction in EOC risk among patients who underwent BS (OR=0.48; 95% CI=0.33–0.69; p<0.001). On the other hand, in the analysis of 4 studies (5,745,887 patients) that examined US, the association with EOC risk was not significant despite the protective trend (OR=0.82; 95% CI=0.64–1.06; p=0.12).

Conclusion: Our results indicate BS is an effective strategy for reducing the risk of sporadic EOC, but the results did not lead to the same conclusion for patients who underwent US. When a candidate or patient is undergoing a hysterectomy or has other benign diseases, prophylactic BS may be a safe surgical procedure that carries future benefits in terms of EOC risk.

Keywords: Salpingectomy; Ovarian Epithelial Cancer; Meta-Analysis; Ovarian Function

Synopsis

The present study aimed to assess the effectiveness of salpingectomy, bilateral salpingectomy (BS), and unilateral salpingectomy in mitigating the risk of epithelial ovarian cancer (EOC). The results of our investigation revealed that BS emerged as a highly efficacious approach for reducing the incidence of EOC.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability Statement

The data used and analyzed during the study will be made available upon reasonable request made through the corresponding author.

Author Contributions

Conceptualization: L.R.; Data curation: T.Y., S.H., F.P., Z.T., L.R.; Formal analysis: T.Y., S.H., F.P., Z.T., L.R.; Investigation: T.Y., F.P., Z.T.; Methodology: T.Y., Z.T., L.R.; Project administration: L.R.; Software: S.H.; Supervision: L.R.; Writing - original draft: T.Y.; Writing - review & editing: L.R.

INTRODUCTION

Epithelial ovarian cancer (EOC) has a poor prognosis with the highest mortality among all gynecologic malignancies [1]. Approximately 30% to 50% of women diagnosed with ovarian cancer (OC) survive at least 5 years after diagnosis [2]. Given the absence of effective screening strategies for OC, it becomes especially important to either prevent OC or detect it in its early stages. In 2000, abnormal epithelial cells were discovered in fallopian tube specimens obtained by risk-reducing salpingo-oophorectomy (RRSO) [3]. As a consequence, the presence of the fallopian tube has been proposed as a connecting link in the chain of events leading to the development of high-grade serous ovarian carcinoma (HGSOC), a serous tubal intraepithelial carcinoma (STIC) [4]. Whole-exome and tumor evolutionary analysis revealed that the majority of tumor-specific alterations in HGSOC, mostly affecting BRCA, TP53, and PTEN, are already present in STIC and confirmed STIC as the precursor lesions [5]. In 2010, Kurman and Shih [6] provided additional cogent evidence that HGSOC may originate from fallopian tubes. The suggested pathological pathway has created new prospects for reducing the risk of EOC by means of salpingectomy. In high-risk populations, such as women carrying BRCA mutations or other homologous recombination (HR) gene mutations, the most effective method to decrease the likelihood of EOC is to opt for RRSO [7]. However, only 20% of OC patients are carriers of HR gene mutations [8], and less than 25% of them have BRCA1/2 mutations [9]. Currently, RRSO is not recommended for the general population or women who do not have an HR gene mutation. Therefore, preventing OC in the general population continues to be a major problem.

Because HGSOC may originate from fallopian tubes, clinicians began to notice the role of opportunistic salpingectomy (OS) in preventing OC. Bilateral salpingectomy (BS) has been shown to reduce OC risk in cohort studies and systematic reviews [10,11]. Additionally, Yoon et al. [12] reported a 45% reduction in risk assuming OS would prevent all OCs. Notably, this procedure did not increase the rate of surgery-related complications if performed by experienced surgeons [13]. Two studies showed that opportunistic BS (OBS) could potentially offer cost-effectiveness, assuming a 50% reduction in OC risk and the low cost associated with OS [14,15]. Therefore, OBS is recommended by the Society of Gynecologic Oncology and the American College of Obstetricians and Gynecologists as a proposed main strategy for OC prevention [16]. Given that a hysterectomy performed alongside salpingectomy is just as safe as a hysterectomy on its own, and considering that salpingectomy decreases the occurrence of EOC, it is advisable to recommend salpingectomy. However, the efficacy of unilateral salpingectomy (US) in reducing the risk of OC is rarely mentioned. Only one study reported an inverse association between US and OC, however, the risk reduction observed in this case was less significant than that observed with OBS [17]. It's also important to highlight that previous studies did not incorporate Asian populations.

The hormonal activity of postmenopausal ovaries allows for the production of estrogen and androgen [18]. Retaining the ovaries in peri- and postmenopausal women has been found to decrease the likelihood of developing coronary heart disease and experiencing hip fractures compared to undergoing oophorectomy [19]. Research indicates that ovulation is a prevalent contributing factor in the majority of OC cases [20]. Inflammation may serve as one mechanism in the pathogenesis of OC, with ovulation exposing the reproductive tract to an inflammatory environment [21]. Consequently, early menopause cannot only decrease the frequency of ovulations but also mitigate the risk of EOC.

In this study, we examined the effectiveness of BS and US in reducing EOC risk, including in Asian women. There are different views on whether salpingectomy has an impact on ovarian reserve. More studies support that phosphate buffered saline has no significant effect on ovarian function [22,23]. So, we also aimed to evaluate the safety of salpingectomy compared to tubal ligation or hysterectomy alone.

MATERIALS AND METHODS

1. Search strategy

From the inception of databases, all databases were searched; with the latest study available at the time of the search in September 2021. In order to search PubMed, MEDLINE (OvidSP), Cochrane Library, Embase (OvidSP), and Web of Science (WOS), we systematically searched each electronic database for “epithelial ovarian cancer”, “salpingectomy”, “tubectomy”, “tubal excision” and related terms in the title, abstract and keywords. Using www.clinicaltrials.gov, we searched for trials that were either in progress or were completed in September 2021 but had not been published yet. References to relevant literature were also searched to avoid omissions. References to conference reports were also examined, but no conference reports were included. Additionally, no authors were contacted. Due to the lack of trials on this topic, no prospective studies or randomized controlled trials (RCTs) were included in this analysis. Furthermore, non-English language papers were excluded, as were studies that did not fulfill the Population/Participants, Intervention, Comparison, Outcomes, and Study (PICOS) criteria. The protocol for Preferred Reporting Items for Systematic Reviews and Meta-analyses was followed in this investigation [24]. A prospective protocol was registered in PROSPERO, CRD42021287064 (<https://www.crd.york.ac.uk/prospero/>).

2. Selection criteria

Research was selected based on the following criteria: 1) participants (P) included women who had undergone hysterectomy or other gynecological procedures for benign conditions; 2) intervention (I) included salpingectomy (including bilateral, unilateral, and unreported bilateral or unilateral); 3) control (C) included women who had not undergone salpingectomy; 4) outcome measure (O) included the prevalence of EOC; and 5) study type (S) included RCTs, population-based case-control studies, cohort studies, nested case-control studies and case series. Editorial commentaries, incomplete trials, non-English-language articles, protocol papers, reviews, articles with incomplete or no data, duplicate articles, and animal studies were excluded.

3. Data extraction

The analyses relied on studies/reports published in the databases; hence, no ethical approval was needed. A researcher (Yuting Tang) extracted the data and the principal investigator (RongHua Liu) verified it. Two reviewers (Pingyin Fu and Haiying Sun) independently screened all studies and checked them for duplicate articles. The full text of the articles identified after screening was further reviewed by the same 2 authors who independently assessed their eligibility. Disagreements were resolved by consensus-based discussion with other authors (Ling Zhang and Ting Zhou).

4. Quality assessment

For cohort studies and case-control studies, the Newcastle-Ottawa Scale was used to evaluate quality and bias. The assessment of case-control studies included the following:

control selection and definition, representativeness of cases, competent definition of cases (selection, 0–4); analyzing or designing a comparison of cases and controls (comparability, 0–2); and cases and controls were assessed using the same method, and nonresponses were recorded (exposure, 0–3). The assessment of cohort studies included the following: Identifying the nonexposed cohort, estimating exposure, and demonstrating that the outcome of interest did not exist at the beginning of the study (selection, 0–4); design or analysis-based comparability of cohorts (comparability, 0–2); and a long-term follow-up and assessment of cohorts (outcome, 0–3). Although no defined criteria exist to discriminate between studies of high and low quality, it has been suggested that a 5-point threshold be used to identify studies with a low risk of bias.

5. Statistical analysis

To test for heterogeneity between studies, I^2 was used, which calculates the proportion of total variation in effect sizes attributed to heterogeneity rather than sampling variance. In this study, in cases where $I^2 > 50\%$, we used a random-effects model, while in cases where $I^2 \leq 50\%$, we used a fixed-effects model. The effect estimates were ORs with 95% confidence intervals (95% CIs). A meta-analysis was conducted using REVIEW MANAGER 5.4. Subgroup analyses were conducted for different study types, such as cohort studies or case-control studies.

RESULTS

1. Study selection

A total of 427 relevant articles were searched, of these, 248 articles remained after the removal of duplicate articles ($n=176$) and non-English articles ($n=3$). Additionally, following a review of the titles and abstracts, 230 articles that did not meet the PICOS criteria were removed. A full review of the remaining 18 full-text articles resulted in the exclusion of a total of 11 articles that failed to meet the inclusion criteria, including 2 editorial comments, 1 ongoing trial, 1 cost-effectiveness analysis, 2 model analyses, 3 review articles, 1 report on the characteristics of ovarian clear cell carcinoma, and 1 report on complications and ovarian reserve. Finally, 6 articles (6,896,589 patients) that met the requirements were included [25–30]. The flow chart of the literature screening process is shown in **Fig. 1**. The final included articles are summarized in **Table 1**. The risk-of-bias assessment is presented in **Table 2** and **Table S1**. Six articles with a score of 7 or more were included, while one article was excluded for its low quality [31]. All the studies we included were either retrospective cohort studies or case-control studies, as there were no RCTs identified.

2. Rate of EOC and salpingectomy

Following the screening process, 6 studies that explored the correlation between salpingectomy and EOC were examined and analyzed, with significant heterogeneity among these studies ($p < 0.001$ $I^2 = 84\%$). The heterogeneity could be attributed to the fact that all these studies were case-control studies or cohort studies. A significant difference was observed in the rate of EOC between the control group and the salpingectomy group ($OR = 0.63$; 95% $CI = 0.45–0.89$); $p = 0.007$) (**Fig. 2A**). Following a subgroup analysis aimed to distinguish between case-control and cohort studies, it was found that there was no statistical heterogeneity between the groups in the case-control studies ($p = 0.19$; $I^2 = 35\%$) (**Fig. 2B**). These findings demonstrate that OS lowers the incidence of EOC.

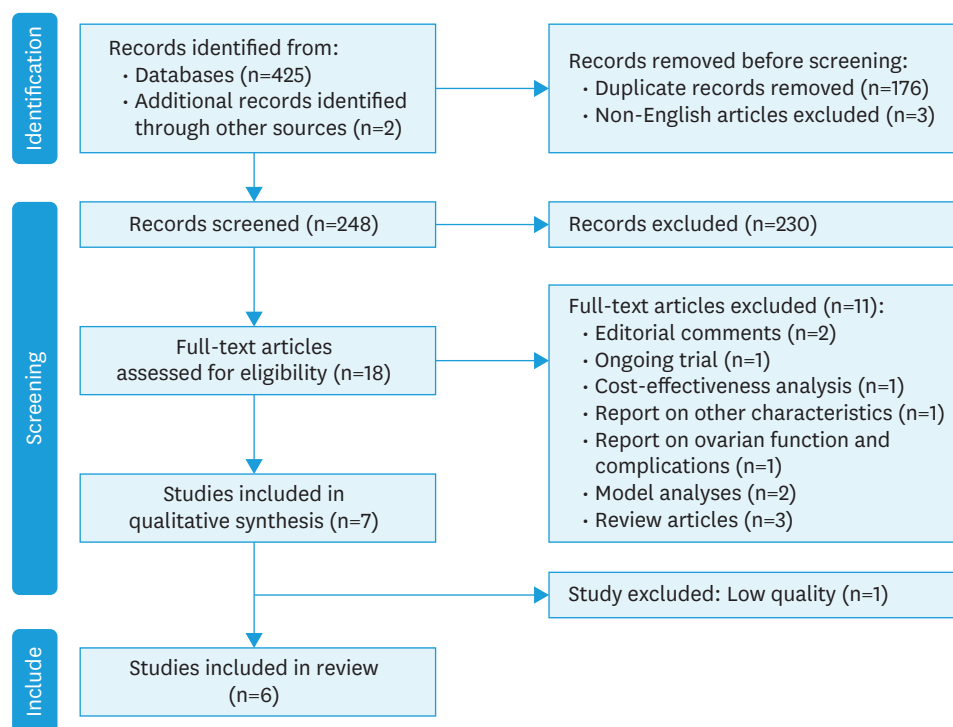


Fig. 1. Flow diagram illustrating the literature search process.

Table 1. Characteristics of studies included in the meta-analysis

| Study | Year | Study design | Country | Time period | Follow-up duration (yr) | Total | Cases of event | Cases of control | Outcome | Outcome measure | Result | CI | Covariates |
|------------------------------|------|--|-------------|-------------|-------------------------|-----------|------------------------|--|---|-----------------|--------|-------------|---|
| Chen et al. [25] | 2018 | Institutional case-control | China | 2007–2017 | 10 | 587 | 198 (EOC, PPC) | 389 (clinical characteristics matched) | Without a history of salpingectomy | OR | 2.08 | 1.340–3.227 | Age, children number, marital status, education |
| Darelius et al. [26] | 2021 | Nationwide case-control | Sweden | 2008–2014 | 6 | 11,060 | 1,033 (EOC type I) | 10,027 (EOC type I) | History of salpingectomy | OR | 1.16 | 0.75–1.78 | Endometriosis, PID, |
| | | | | | | 32,080 | 3,007 (EOC type II) | 29,073 (EOC type II) | | | 0.62 | 0.45–0.85 | hysterectomy, tubal ligation |
| Falconer et al. [27] | 2015 | Nationwide population-based cohort | Sweden | 1973–2009 | 36 | 5,452,170 | 3,051 (BS) | 5,449,119 (unexposed population) | Ovarian cancer, tubal cancer | HR | 0.35 | 0.17–0.73 | Age, prior hysterectomy, prior BSO, OC use, endometriosis, infertility, gravidity, parity |
| Lessard-Anderson et al. [28] | 2014 | Population-based case-control | USA | 1966–2009 | 43 | 582 | 194 (EOC, PPC) | 388 (age-matched) | History of excisional tubal sterilization | OR | 0.36 | 0.13–1.02 | Age, parity, endometriosis, PID, infertility, tubal ligation |
| Madsen et al. [29] | 2015 | Nationwide register-based case-control | Denmark | 1982–2011 | 29 | 207,930 | 13,241 (EOC) | 194,689 (age-matched) | History of BS | OR | 0.58 | 0.36–0.95 | Age, education, parity |
| van Lieshout et al. [30] | 2021 | Nationwide population-based case-control | Netherlands | 1990–2017 | 27 | 42,647 | 18,961 (salpingectomy) | 23,686 (nevus) | History of salpingectomy | HR | 0.78 | 0.40–1.50 | Age, prior BSO |

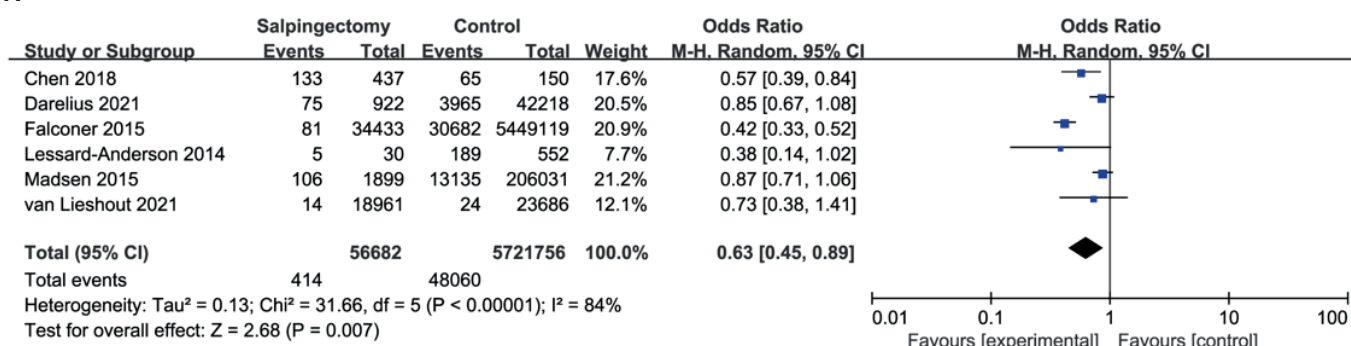
BS, bilateral salpingectomy; BSO, bilateral salpingo-oophorectomy; CI, confidence interval; EOC, epithelial ovarian cancer; HR, hazard ratio; OC, ovarian cancer; OR, odds ratio; PID, pelvic inflammatory disease; PPC, primary peritoneal cancer.

Table 2. Qualitative synthesis risk assessment and quality assessment scale using NOS for case-control studies

| Study | Year | Selection | | | | Comparability | | Exposure | | Scores |
|------------------------------|------|------------------------------|---------------------------------|------------------------|------------------------|--|---------------------------|---|-------------------|--------|
| | | Defining cases appropriately | Representativeness of the cases | Selections of controls | Definition of controls | Comparability control for important factor | Ascertainment of exposure | The same method of ascertainment for cases and controls | Nonresponses rate | |
| Chen et al. [25] | 2018 | ★ | ★ | | ★ | ★★ | ★ | ★ | ★ | 8 |
| Darelius et al. [26] | 2021 | | ★ | ★ | ★ | ★★ | ★ | ★ | ★ | 8 |
| Lessard-Anderson et al. [28] | 2014 | | ★ | ★ | ★ | ★★ | ★ | ★ | ★ | 8 |
| Madsen et al. [29] | 2015 | | ★ | ★ | ★ | ★ | ★ | ★ | ★ | 7 |
| van Lieshout et al. [30] | 2021 | | ★ | ★ | ★ | ★★ | ★ | | ★ | 7 |

NOS, Newcastle-Ottawa Scale.

A



B

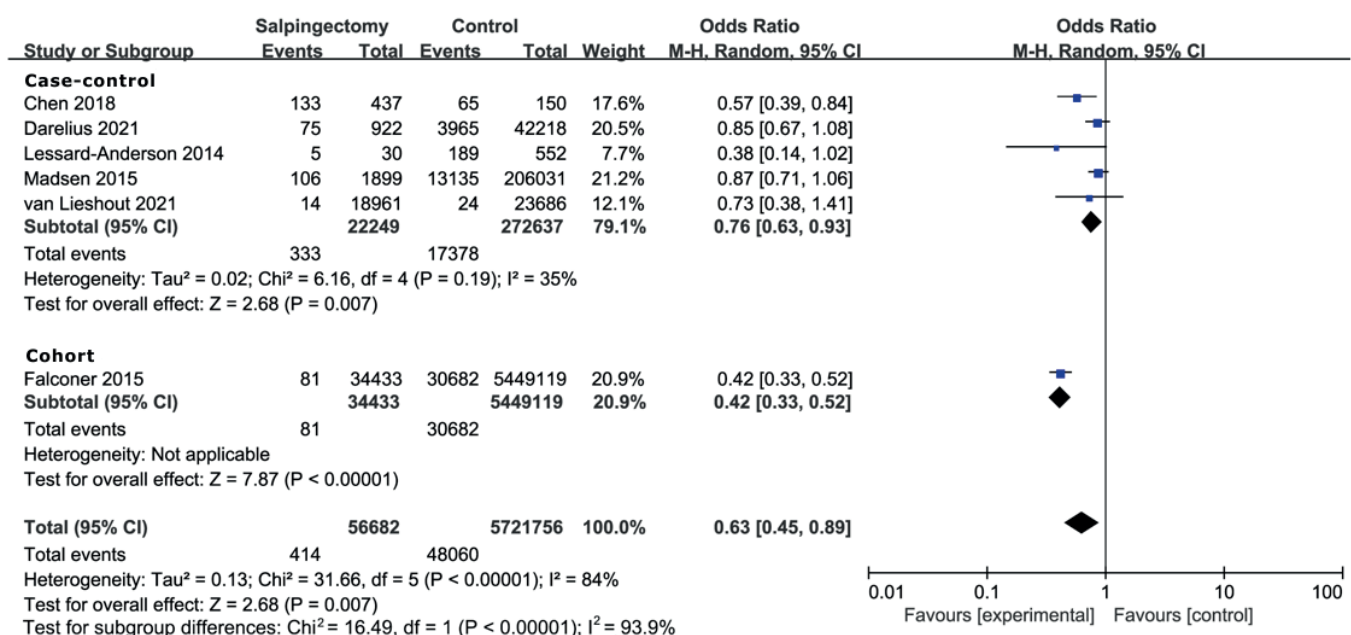


Fig. 2. A forest plot showing the association between salpingectomy and epithelial ovarian cancer risk derived from the final 6 studies. (A) Random-effects model. (B) Subgroup analysis. CI, confidence interval.

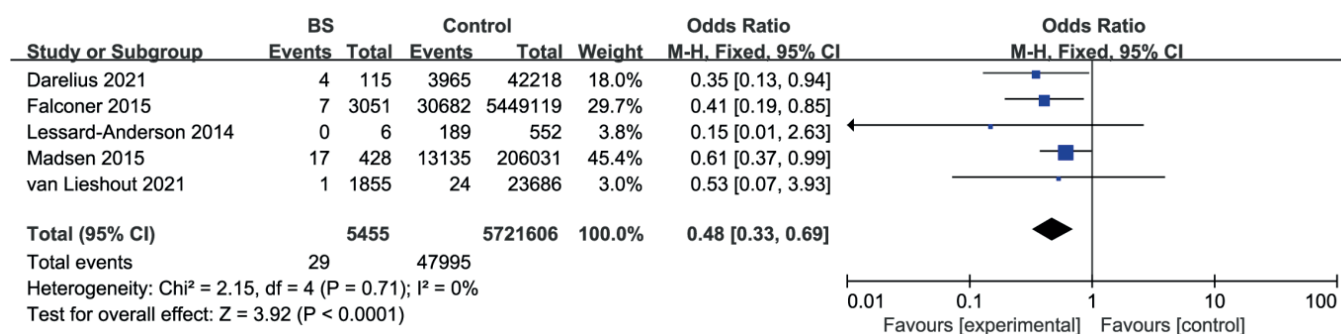


Fig. 3. A forest plot depicting the association between BS and epithelial ovarian cancer risk in 5 case-control studies. BS, bilateral salpingectomy; CI, confidence interval.

3. Rate of EOC and BS

Next, we proceeded to analyze the morbidity of EOC after BS. Among the final 6 eligible studies, 5 articles (294,886 patients) were case-control studies. All the case-control studies had data on BS, and therefore, the strength of the correlation between BS and the incidence of EOC was analyzed. The studies did not show statistical heterogeneity ($p=0.712$; $I^2=0\%$), so a fixed-effects model was applied. A significant reduction in OC morbidity was observed in the BS group compared to the control group (OR=0.48; 95% CI=0.33–0.69; $p<0.001$) (**Fig. 3**). This indicates the effectiveness of BS in reducing the morbidity associated with EOC.

4. Rate of EOC and US

Furthermore, we investigated whether the US was associated with EOC in 4 articles and found that a significant amount of heterogeneity was found among the 4 studies ($p=0.03$; $I^2=67\%$). Due to the small number of patients in one study, there was a significant difference in OC rates between the salpingectomy and control groups, although it was not statistically significant (OR=0.82; 95% CI=0.64–1.06; $p=0.12$) (**Fig. 4A**). To distinguish between case-control and cohort studies, we conducted subgroup analysis and found no statistical heterogeneity among studies involving case-controls ($p=0.773$; $I^2=0\%$) (**Fig. 4B**).

DISCUSSION

In this systematic review and meta-analysis, the final case-control and cohort studies present robust evidence supporting the risk-reducing effect of salpingectomy on EOC. Women who underwent salpingectomy had a 37% lower risk of developing EOC compared to the control group, while women who underwent BS were 52% less likely to develop EOC. Our findings may help professionals and women choose whether BS or US should be performed at the time of hysterectomy or other surgeries due to benign causes.

OS or tubal ligation can reduce the incidence of EOC and is commonly accepted by clinicians and even recommended as a preventive measure in some countries [32]. Animal experiments have also confirmed this observation [33]. To obtain more robust evidence confirming the potential reduction in OC incidence through these strategies, conducting prospective randomized trials with a larger number of patients and with extended follow-up periods is needed. Nevertheless, patients are less likely to agree to and participate in such clinical trials [34]. Therefore, retrospective analyses and cohort studies on prophylactic surgical strategies may be the main method to evaluate whether OS or tubal ligation can reduce EOC risk. In

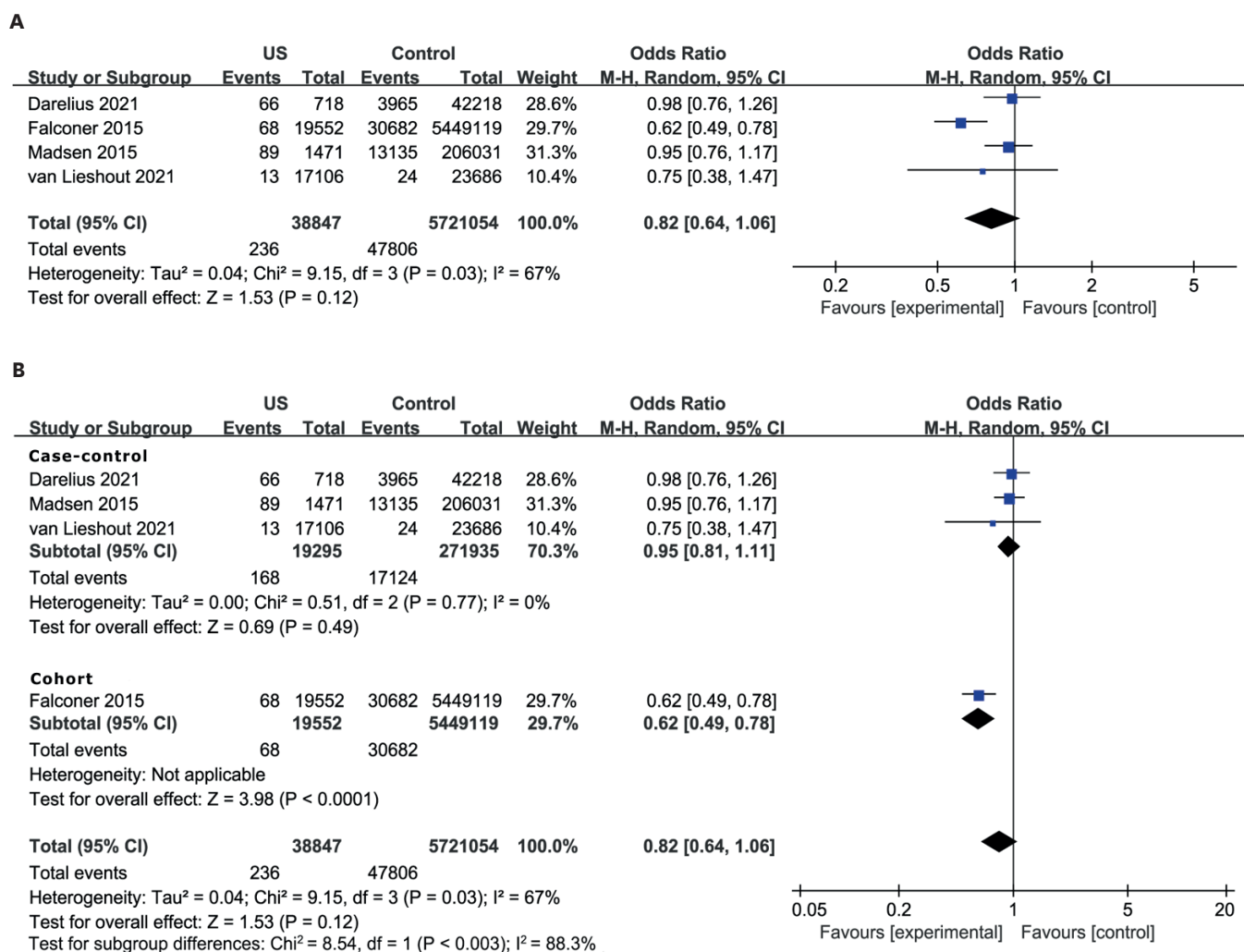


Fig. 4. A forest plot of the final 6 studies comparing unilateral salpingectomy with epithelial ovarian cancer risk. (A) Random-effects model and (B) subgroup analysis. CI, confidence interval; US, unilateral salpingectomy.

addition, there are a number of studies that investigated factors influencing decision-making process around OS [35]. Type of institution, different level of hospitals, work experience and gynecology trainees all affect whether to choose OS.

In order to better understand how OS reduces EOC incidence, we analyzed patients with salpingectomy (no distinction between US and BS) and found that salpingectomy can significantly reduce the incidence of EOC. When BS and US were analyzed separately, we found that only BS significantly reduced the incidence, whereas, no significant effect of US on reducing EOC risk was observed, despite an observable trend in a protective direction ($OR=0.82$; $95\% CI=0.64-1.06$). Only one study showed that the US could reduce the incidence of OC [28]. Early recommendation of bilateral salpingo-oophorectomy (BSO) for BRCA mutation carriers is advised as a preventive measure against OC. The risk of overall EOC does not appear to be influenced by the age or year of tubal ligation (cut-off: 35 years) [29]. Additional studies are required to better examine this association US and the incidence of OC. In our analysis, we did not distinguish the histologic type of EOC. In one of the included studies [26], it was observed that salpingectomy was associated with a

lower incidence of type II EOC, whereas no such association was observed for type I.. Recent studies suggest that the fallopian tubes, particularly in the case of HGSC, may potentially be the origin of EOC [36]. An alternative theory proposes that endometriosis-associated OC could arise from oncogenic mutations in eutopic endometrial glandular epithelial cells that have been implanted in the ovary through retrograde menstrual blood flow, for which the fallopian tubes act as a pathway in this menstrual blood reflux [37]. Currently, hysterectomy is not supported as a preventative measure for OC, however, it can reduce the incidence of endometrioid-invasive OC [38]. This could be attributed to the absence of endometrial tissue to stimulate the ovary after hysterectomy, which is similar to the role of tubal ligation. Based on these pathophysiological theories, it can be argued that salpingectomy may serve as a protective measure against the development of EOC. This is in line with our results of the risk-reducing effect of BS.

Due to the lack of statistics from other countries, existing nationwide population-based studies are mostly from Europe and the USA. In one study, a single-center case-control study from Tianjin, China [25], was included in the meta-analysis after a rigorous qualitative synthesis. Nevertheless, the other 5 studies were from Europe and the USA. Another population-based cohort study from Asia came to quite different conclusions. In their study, women who had undergone both hysterectomy and US had the greatest risk, with an adjusted hazard ratio of 3.86 (95% CI=2.56–5.84) [31]. However, women with BS were less likely to develop OC [39]. Inexplicably, after hysterectomy, these women (of whom, over 50% had endometriosis) were significantly more likely to develop OC. Given the potential quality concerns identified for this study, we opted not to include it in our analyses. Additionally, future studies should investigate whether disparities exist based on race. Although salpingectomy has shown consistent protective benefits against EOC in European and American populations, studies from other geographical regions and different ethnic groups are still necessary. This can be addressed by establishing or improving healthcare registry databases across a wider range of countries and geographical regions.

The rationale for performing US instead of BS in some centres could be ectopic pregnancy or hydrosalpinx [30]. In our analysis we found no significant difference of developing EOC after undergoing US. Although one side of fallopian tube has been removed, the other side can still function physiologically and pathologically. If existing, abnormal epithelial cells still have the potential to invade ovary and develop EOC.

Our work had several limitations. Four of the 6 articles we included in our study were nationwide case-control studies. However, there was still one case-control study at a single institution and one population-based study. Although we performed quality assessments and showed no statistical evidence of bias, the meta-analysis still suffered from bias, as the clinical observations were retrospective. No definitive conclusion regarding the occurrence of OC was found in the studies that examined patients who had undergone BS or tubal ligation. Hence, arriving at a definitive conclusion regarding whether BS or tubal ligation effectively reduces the risk and likelihood of OC remains challenging. Whether these treatment procedures influence ovarian function or reserve requires longer observation. Although researchers are well aware that it is very difficult to carry out prospective clinical trials exploring the role of prophylactic salpingectomy, in 2019, a national register-based RCT was conducted to evaluate the risks and benefits of OS, which will be followed up for up to 30 years [40]. The outcomes of this trial will serve as a valuable confirmation of our findings.

In conclusion, our results in this study highlight the advantages of BS in reducing EOC risk in the general population. Women who do not have plans for future childbearing are recommended to consider BS when undergoing hysterectomy and other abdominal surgeries or as an option for sterilization. The long-term impact of BS on reducing OC risk needs to be investigated further.

SUPPLEMENTARY MATERIAL

Table S1

Qualitative synthesis risk assessment and quality assessment scale using NOS for cohort studies

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