European Journal of Gynaecological Oncology

*Eur. J. Gynaecol. Oncol.* **2022**; 43(1): 56–63
http://doi.org/10.31083/j.ejgo4301006

*Systematic Review*

# The incidence and risk factors for ovarian metastasis and overall survival with ovarian preservation for early-stage adenocarcinoma of the cervix-A meta-analysis

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Academic Editor: Enrique Hernandez

Submitted: 15 August 2021 Revised: 27 November 2021 Accepted: 30 November 2021 Published: 15 February 2022

**Abstract**

**Objective**: To compare the incidence of ovarian metastasis (OM) in early stage adenocarcinoma (AC) and squamous cell carcinoma (SCC) of the cervix, evaluate the overall survival with ovarian preservation and determine risk factors of OM for early stage AC. **Data sources, methods of study selection**: We searched the Cochranes database, Embase, and PubMed for publications to November 2020. The articles reporting the incidence, risk factors and overall survival of OM in AC were included. Articles that lacked sufficient data of the odds ratios (ORs) and 95% confidence intervals (CIs) were excluded. A fixed effects model was used to calculate OR and 95% CIs. Eggers test and Funnel plot were used to test the publication bias. Forest plots was used to present and synthesise results. **Tabulation, integration and results**: In the meta-analysis, the incidence of OM of AC was higher than that of SCC (OR 5.68, 95% CI 4.40–7.32, $I^2$ = 28.1%) in stage IA-IIB. The incidence of OM was 0% in stage IA, 2.72% in stage IB, 5.95% in stage IIA, and 12.86% in stage IIB AC. Ovarian preservation was not significantly associated with OS (OR 0.53, 95% CI 0.35–0.80, $I^2$ = 37.8%) in early stage of AC. We found seven risk factors for OM: deep stromal invasion (OR 8.80, 95% CI 3.20–24.23, $I^2$ = 0%), corpus uteri invasion (OR 6.29, 95% CI 3.36–11.77, $I^2$ = 21.8%), tumor size >4 cm (OR 3.78, 95% CI 1.86–7.69, $I^2$ = 30.5%), FIGO stage IIA (OR 3.67, 95% CI 1.98–6.81, $I^2$ = 0%), FIGO stage IIB (OR 4.31, 95% CI 2.74–6.77, $I^2$ = 0%), FIGO stage II (OR 3.99, 95% CI 2.49–6.41, $I^2$ = 0%) and lympho-vascular space invasion (OR 2.90, 95% CI 1.36–6.17, $I^2$ = 0%). **Conclusions**: Ovarian preservation is only recommended in stage IA and stage IB AC without risk factors, but not reasonable for stage IIA and IIB AC. Both stage IIA and IIB are risk factors for OM in early stage AC.

**Keywords:** Adenocarcinoma of cervix; Ovarian preservation; Ovarian metastasis; Risk factors

## 1. Introduction

Secondary to the increase in early screening, the incidence of cervical squamous cell carcinoma (SCC) has decreased while the incidence of cervical adenocarcinoma (AC) is increasing [1,2]. More than 33% of AC patients were younger than 40 years old [3]. Some studies have found that the incidence of ovarian metastasis (OM) for AC was higher than that for SCC by 4.5%–7.8% [4–10], but some studies also reported that the incidence of OM in early AC and SCC were similar [11]. It is still controversial whether young patients with early AC should have ovarian preservation. Studies have shown that people who underwent early oophorectomy had a higher mortality rate if they had not received estrogen therapy [12,13]. We identified the difference in the incidence of early AC and SCC and the overall survival (OS) of ovarian preservation for early AC through meta-analysis. We also identified the risk factors of OM in early AC.

## 2. Materials and methods

### *2.1 Search method*

Cochranes database, Embase, and PubMed database were searched to November 2020: "cervical cancer", "adenocarcinoma of the cervix", "ovarian metastasis", and "ovarian preservation" were used as search terms in the title or abstract. The language was limited to "English".

### *2.2 Criteria for inclusion and exclusion*

The criteria for inclusion were as follows: (1) The diagnosis of cervical AC. (2) Prospective or retrospective cohort. (3) The sample size greater than 20. (4) Studies reported the incidence of OM for SCC and AC. (5) Studies that included the survival rate of patients with removal and preservation of ovaries for AC. (6) Studies that reported the risk factors for OM in AC.

The criteria for exclusion were as follows: (1) The sample size was less than 20. (2) Lack of sufficient data of the odds ratios (ORs) and 95% confidence intervals (CIs). (3) Overlapping or duplicate articles.

### 2.3 Data extraction

Data extraction was performed by one author and checked by a second author. The information extracted from each study was as follows: author, country, total number of patients, year of publication, FIGO stage, number of patients undergoing oophorectomy and ovarian preservation, incidence of OM.

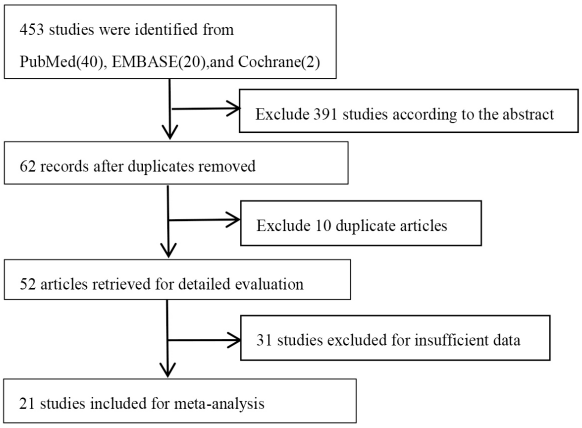


**Fig. 1. The flow diagram for selection of literature.**

### 2.4 Quality assessment

The quality of the included studies was evaluated independently by the use of Newcastle-Ottawa Quality Assessment Scale. High-quality studies were defined as final score $\geq$6.

### 2.5 Statistical analysis

Stata 12.0 (STATA, College Station, TX; Computing Resource Center, Santa Monica, CA, USA) was used for the statistics of ORs and 95% CIs. Heterogeneity was assessed by Cochran's-Q test and $I^2$ statistics. Heterogeneity was regarded as statistically significant when $I^2 > 50\%$ and the $p$-value $< 0.05$ in Cochran's-Q test. If needed, a random-effects model was chosen.

### 2.6 Publication bias and sensitivity analysis

Eggers test was used to assess for publication bias. Publication bias was defined as $p < 0.05$. Funnel plot was also used to test the publication bias. Sensitivity analysis was assessed by deleting one study at one time to examine its effect on the final result.

### 2.7 FIGO stage

FIGO 2018 classification was used when abstracting the information from the selected articles. The FIGO stage was adjusted to 2018 classification if the articles were published before 2018.

## 3. Results

### 3.1 Search results and study features

The flow diagram for literature selection is shown in Fig. 1. Eleven studies were obtained in the meta-analysis for the comparison of the rate of the ovarian metastasis for AC and SCC [4–11,14–16]. Six studies were included in the meta-analysis for the overall survival with ovarian preservation in AC [17–22]. Twelve studies were included for the risk factors of ovarian metastasis in AC [5–7,9,10,19,20,23–27] (Table 1, Ref. [4–11,14–26]).

### 3.2 Quality assessment and publication bias of the included studies

The score of the Newcastle-Ottawa Quality Assessment Scale is showed in Table 2 (Ref. [4–11,14–26]). For the comparison of the incidence of OM for early AC and SCC, Funnel plot showed a low risk of publication bias (Fig. 2D, Eggers test: $p = 0.079$). Sensitivity analysis showed no significant change on the final result after one study was deleted (Fig. 2E). For the survival outcome of ovarian preservation, Funnel plot also showed a low risk of publication bias (Fig. 3C, Eggers test: $p = 0.625$). Sensitivity analysis showed no significant change on the final result after one study was deleted (Fig. 3D). For the risk factors of OM for early stage AC, $p$ value of Eggers test for the included studies were as follows: corpus uteri invasion $p = 0.246$, deep stromal invasion $p = 0.716$, age >45 $p = 0.248$, LVSI $p = 0.403$, tumor size >4 cm $p = 0.536$, tumor grade $p = 0.901$, FIGO IIA $p = 0.223$, FIGO IIB $p = 0.264$, and FIGO II $p = 0.213$.

### 3.3 Comparison of the incidence of OM in early AC and SCC

A total of 21,466 patients (AC 3711; SCC 17,755) who underwent hysterectomy and oophorectomy could be obtained from the 11 studies. The incidence of OM for AC was higher than that for SCC in stage IA-IIB (OR 5.68, 95% CI 4.40–7.32, $I^2 = 28.1\%$) (Fig. 2A). In the subgroup, a total of 772 patients with AC and 3867 patients with SCC from 5 studies were included to compare the incidence of OM for AC and SCC in stage I. A total of 2597 patients (AC 289; SCC 2308) from 4 studies were obtained to compare the incidence of OM for AC and SCC in stage II. The incidence of OM in AC was higher than that of SCC in stage I (OR 8.40, 95% CI 4.15–17.01, $I^2 = 19.7\%$) (Fig. 2B) and II (OR 7.31, 95% CI 4.33–12.35, $I^2 = 0\%$) (Fig. 2C).

Overall, the incidence of OM in the AC and SCC group were 3.85% and 0.68% respectively. In the AC group, the incidence of OM was 0% in stage IA, 2.72% in stage IB, 5.95% in stage IIA, and 12.86% in stage IIB. In the SCC group, the incidence of OM was 0% in stage IA, 0.34% in stage IB, 0.8% in IIA, and 2.25% in stage IIB (Table 1).

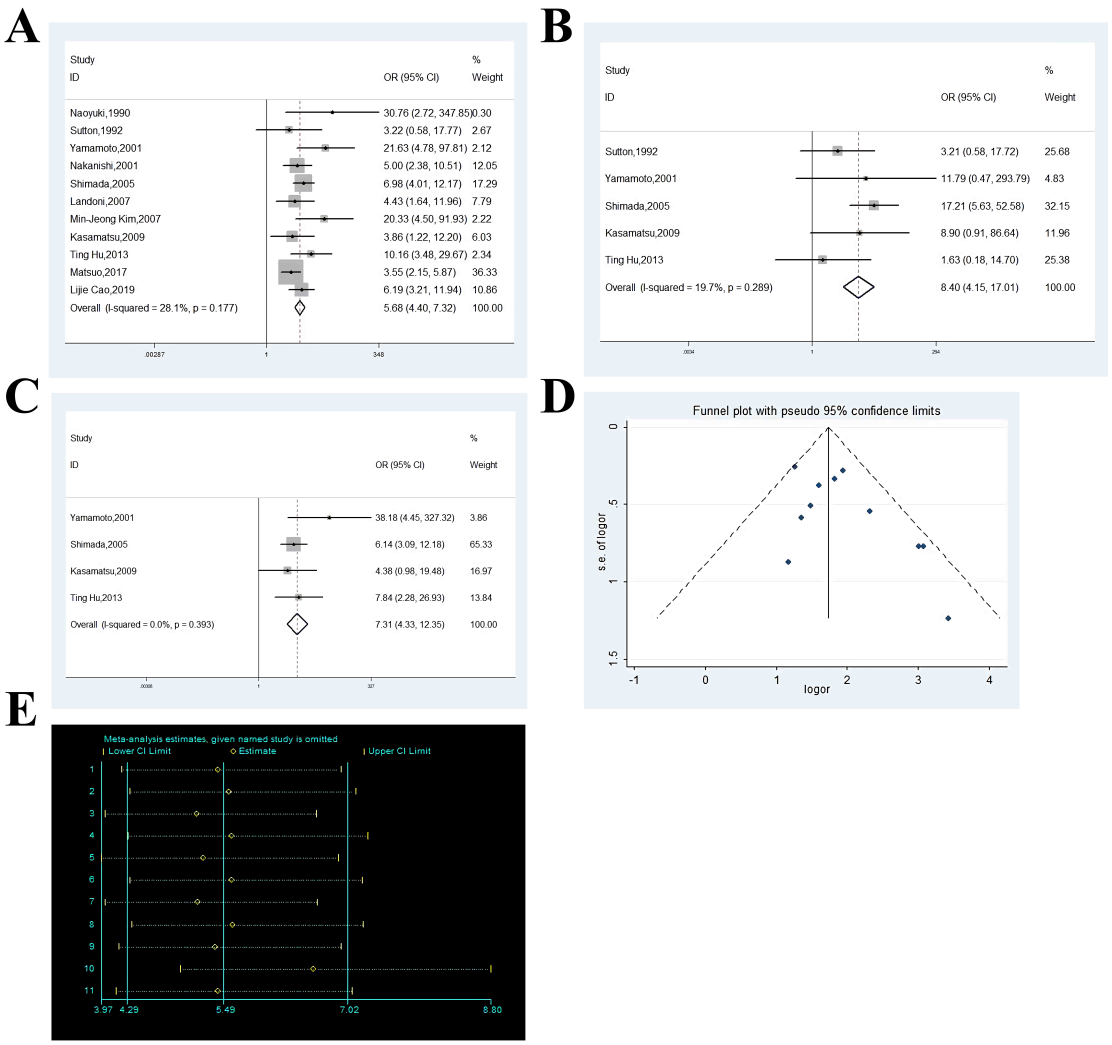


**Fig. 2. Comparation of the rate of OM between AC and SCC.** (A) Forest plots of comparation of the rate of OM between AC and SCC in stage IA–IIB. (B) Forest plots of comparation of the rate of OM between AC and SCC in stage I. (C) Forest plots of comparation of the rate of OM between AC and SCC in stage II. (D) Funnel plot of the 11 included studied showed a low risk of publication of bias. (E) Sensitivity analysis showed no significant change on the final result after one studies was deleted.

### *3.4 Survival outcome of ovarian preservation*

Ovarian preservation occurred in 930 patients while 2493 patients underwent oophorectomy in the 6 studies. Ovarian preservation was not associated with statistically significant OS (OR 0.53, 95% CI 0.35–0.80, $I^2$ = 37.8%) in early stage of AC (Fig. 3A). In the subgroup of stage I, ovarian preservation was not associated with statistically significant OS (stage I: OR 0.46, 95% CI 0.28–0.75, $I^2$ = 0.7%) (Fig. 3B). We did not perform the subgroup analysis in stage II and PFS because of lack of useful data.

Among the 6 studies which included stage IA-IIB AC, the 5-year overall survival rate of patients with or without ovarian preservation was 96.99% and 94.46% respectively ($p$ = 0.084). For stage I, the 5-year overall survival rate of patients with or without ovarian preservation was 97.57% and 95.62% respectively ($p$ = 0.072).

### *3.5 Risk factors of OM for early stage of AC*

A total of 3086 patients with AC were included in the 12 studies. We found seven risk factors for OM: deep stromal invasion (OR 8.80, 95% CI 3.20–24.23, $I^2$ = 0%), corpus uteri invasion (OR 6.29, 95% CI 3.36–11.77, $I^2$ = 21.8%), tumor size >4 cm (OR 3.78, 95% CI 1.86–7.69, $I^2$ = 30.5%), FIGO stage IIA (OR 3.67, 95% CI 1.98–6.81, $I^2$ = 0%), FIGO stage IIB (OR 4.31, 95% CI 2.74–6.77, $I^2$ = 0%), FIGO stage II (OR 3.99, 95% CI 2.49–6.41, $I^2$ = 0%) and lympho-vascular space invasion (OR 2.90, 95% CI 1.36–6.17, $I^2$ = 0%) (Fig. 4A–H). Age >45 (OR 0.95, 95% CI 0.46–1.97, $I^2$ = 0%) and tumor grade (OR 0.93, 95% CI 0.4–2.18, $I^2$ = 0%) were not the risk factors for OM in early stage AC (Fig. 4I,J).

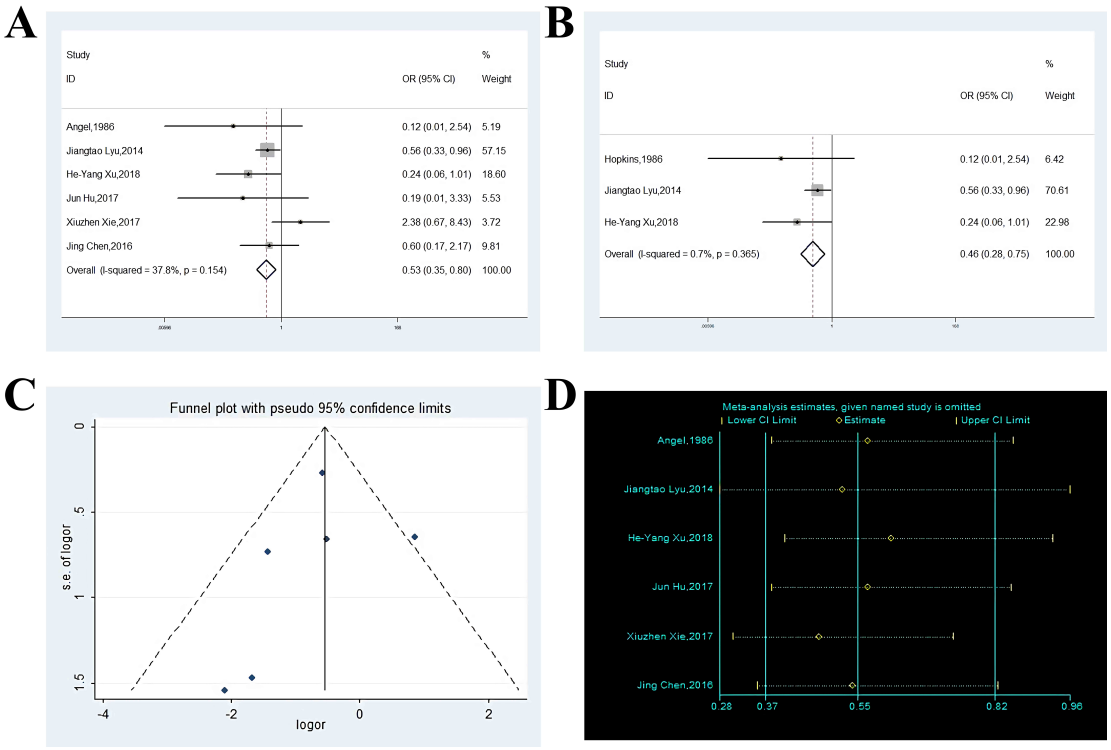


**Fig. 3. Oncological outcomes of ovarian preservation for AC.** (A) Forest plots of the oncological outcomes of ovarian preservation for stage IA–IIB AC. (B) Forest plots of the oncological outcomes of ovarian preservation for stage I AC. (C) Funnel plot of the 6 included studied showed a low risk of publication of bias. (D) Sensitivity analysis showed no significant change on the final result after one studies was deleted.

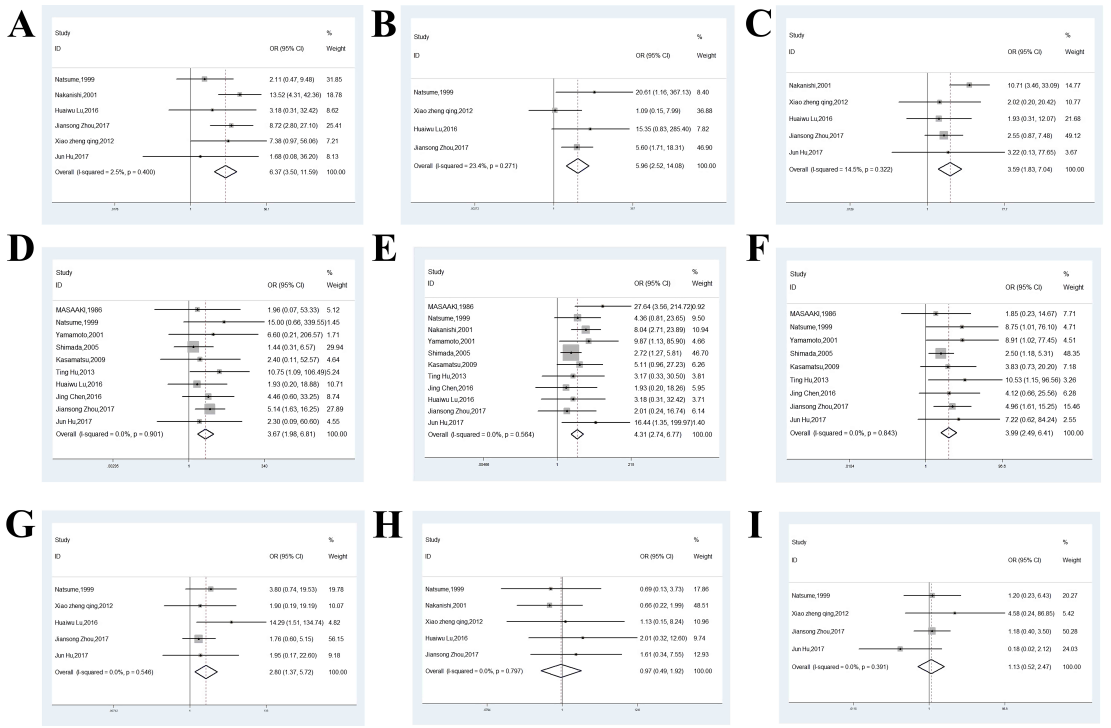


**Fig. 4. Forest plots of 7 risk factors of OM for AC.** (A) Corpus uteri invasion. (B) Deep stromal invasion. (C) Tumor size >4 cm. (D) FIGO stage IIA. (E) FIGO stage IIB. (F) FIGO stage II. (G) Lympho-vascular space invasion. (H) Age >45. (I) Tumour grade.

**Table 1. Characteristic of the included studies.**

| Study | Year | Country | Histology | FIGO stage | Patients | Ovarian | Oophorectomy | Rate of OM | Stage | Rate of OM | Stage | Risk factors of |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | n | preservation | | for SCC | | for AC | | OM for AC |
| Tabata *et al.* [26] | 1986 | Japan | SCC, AC | IB–III | 326 | | 326 | | | 9.75% | IB 7.69%; IIA 0%; IIB 15.38% | |
| Naoyuki *et al.* [4] | 1990 | Japan | SCC, AC | IB–IIIB | 597 | | 597 | 0.19% | | 5.56% | | |
| Sutton *et al.* [11] | 1992 | India | SCC, AC | IB | 990 | | 990 | 0.52% | IB 0.52% | 1.65% | IA 0%; IB 1.65%; | |
| Yamamoto *et al.* [5] | 2001 | Japan | SCC, AC | IB–II | 631 | | 631 | 0.41% | IB 0%; IIA 0%; IIB 0.6% | 8.22% | IA 0%; IB 2%; IIA 0%; IIB 16.22% | |
| Nakanishi *et al.* [6] | 2001 | Japan | SCC, AC | IA–IIB | 1304 | | 1304 | 1.32% | IIB 4.46% | 6.25% | IIB 22.22% | |
| Shimada *et al.* [7] | 2005 | Japan | SCC, AC | IB–IIB | 3471 | | 3471 | 0.80% | IB 0.22%; IIA 0.75%; IIB 2.02% | 5.31% | IB 3.72%; IIA 5.26%; IIB 9.85% | |
| Landoni *et al.* [14] | 2007 | Italy | SCC, AC | IA2–IIA | 1965 | 1695 | 270 | 0.55% | | 2.37% | | |
| Kim *et al.* [8] | 2007 | Korea | SCC, AC | IA1–IIB | 625 | | 625 | 0.42% | | 7.95% | | |
| Kasamatsu *et al.* [9] | 2009 | Japan | SCC, AC | I–IIB | 578 | | 578 | 0.13% | IB 0.36%; IIA 1.96%; IIB 3.1% | 4.92% | IB 3.16%; IIA 0%; IIB 13.64% | |
| Hu *et al.* [10] | 2013 | China | SCC, AC | IB–IIB | 1889 | | 1889 | 0.74% | IB 0.47%; IIA 0.8%; IIB 1.46% | 6.94% | IB 0.77%; IIA 7.69%; IIB 7.14% | |
| Matsuo *et al.* [15] | 2017 | Japan | SCC, AC | IB–IIB | 5697 | | 5697 | 0.73% | | 2.56% | | |
| Cao *et al.* [16] | 2019 | China | SCC, AC | IA2–IIA2 | 5181 | 1496 | 3685 | 0.50% | | 3.07% | | |
| Hopkins *et al.* [17] | 1986 | USA | AC | I–IV | 84 | 8 | | | | | | |
| Lyu *et al.* [18] | 2014 | China | AC | I | 1639 | 577 | 1062 | | | | | |
| Chen *et al.* [19] | 2016 | China | AC | IIB | 159 | 33 | 126 | | | 3.47% | IA 0%; IB 2%; IIA 7.69%; IIB 5.56% | |
| Hu *et al.* [20] | 2017 | China | AC | IIB | 105 | 19 | 86 | | | 2.86% | IA 0%; IB 1.47%; IIA 0%; IIB 16.67% | |
| Xie *et al.* [21] | 2017 | China | AC | IIA | 128 | 15 | 113 | 1.32% | | 0.08% | | |
| Xu *et al.* [22] | 2018 | China | AC | I | 1386 | 278 | 1090 | | | | | |
| Natsume *et al.* [23] | 1999 | Japan | AC | IB–II | 82 | | 82 | | | 12.90% | IB 3.22%; IIA 33.3%; IIB 21.43% | |
| Lu *et al.* [25] | 2017 | China | AC | IA2–IIA2 | 101 | | 101 | | | 4.95% | IA 0%; IB 4.55%; IIA 8.33%; | Grade, LVSI, LMN, tumor size, DSI, UCI |
| Zhou *et al.* [24] | 2012 | China | AC | I–IIB | 312 | | 312 | | | 4.50% | IB 2.3%; IIA 10.81%; IIB 8.33% | UCI, PMI, vaginal infiltration |

OM, ovarian metastasis; LVSI, lympho-vascular space invasion; LMN, lymph node metastasis; DSI, deep stromal invasion; UCI, uterine corpus involvement; PMI, parametrial involvement.

**Table 2. Quality assessment of included studies.**

| Selection | Tabata *et al.* [26] | Toki *et al.* [4] | Sutton *et al.* [11] | Yamamoto *et al.* [5] | Nakanishi *et al.* [6] | Shimada *et al.* [7] | Landoni *et al.* [14] | Kim *et al.* [8] | Kasamatsu *et al.* [9] | Hu *et al.* [10] | Matsuo *et al.* [15] | Cao *et al.* [16] | Hopkins *et al.* [17] | Lyu *et al.* [18] | Chen *et al.* [19] | Hu *et al.* [20] | Xie *et al.* [21] | Xu *et al.* [22] | Natsume *et al.* [23] | Lu *et al.* [25] | Zhou *et al.* [24] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Case definition with independent validation | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Consecutive or obviously representative series of cases | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| community controls | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| No endpoint of disease in controls at start study | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Comparability | | | | | | | | | | | | | | | | | | | | | |
| Study controls for age | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 |
| Study controls for FIGO stage | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 |
| Exposure | | | | | | | | | | | | | | | | | | | | | |
| Ascertainment of exposure from secure record | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Same method and ascertainment for cases and controls | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Same non-response rate for both groups | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Total score | 7 | 7 | 7 | 7 | 9 | 8 | 8 | 9 | 9 | 9 | 9 | 8 | 7 | 8 | 9 | 9 | 9 | 8 | 7 | 9 | 9 |

## 4. Discussion

This study has a large sample size for the comparison of the incidence of OM between AC and SCC. The overall incidence of AC with OM was 3.85%, which was higher than that of SCC (0.68%). The incidence of OM for AC was higher than that of SCC in stage IA–IIB (OR 5.68, 95% CI 4.40–7.32, $I^2$ = 28.1%). In the subgroup meta-analysis of stage I and II, we reached the same conclusion.

We found that the incidence of OM for SCC and AC were both 0% in stage IA so ovarian preservation is appropriate in this group. The incidence of OM for stage IB AC and SCC were not very high (2.73% vs 0.8%) but The incidence of OM for stage IB AC was still higher than SCC. As a result, we suggest that ovaries should be preserved for stage IB patients without risk factors. The incidence of OM for stage IIA and IIB AC was as high as 5.95% and 12.86%, so we do not recommend that patients with stage IIA and IIB AC retain their ovaries. Through meta-analysis, Hongyan Cheng *et al.* [27] believed that ovarian preservation was not recommended for stage IIB, while ovarian preservation for stage I–IIA was reasonable. Among the included studies, the incidence of OM for stage IIA was 3.4% and that for stage IIB was 11.8%. Their sample size was smaller than ours, so there was a difference in the incidence of OM for stage IIA. Their meta-analysis did not separately regard stage IIA and IIB as risk factors.

In the meta-analysis to study the overall survival of ovarian preservation, we only included studies that specifically focused on the overall survival of ovarian preservation for AC, and excluded studies when pathological data for AC was unavailable, as in the study performed by Matsuo [15]. Xie *et al.* [21] found that there was no difference in the 5-year survival rate between patients with ovarian preservation and patients with oophorectomy (75% vs 86.6%; $p > 0.05$) for AC in t stage IB–IIA. For T1N0M0 cervical adenocarcinoma, Xu *et al.* [22] found that oophorectomy group had worse cause-specific survival (5-year 97.1% vs 98.8%, 10-year 95.2% vs 98.0%, $p$ = 0.0370) and overall survival (5-year 97.1% vs 98.8%, 10-year 93.5% vs 96.5%, $p$ = 0.0025). Our meta-analysis found that ovarian preservation was not associated with statistically significant OS. In the sub-group analysis for stage I, we reached similar conclusions. In the existing literature, there is no data for OS of ovarian preservation especially for stage II AC. Due to lack of data, we did not perform a subgroup analysis of stage II. Therefore, whether patients with stage IIA and IIB could undergo ovarian preservation requires further research.

In the meta-analysis of the risk factors for OM in AC, we only included studies on the risk factors of OM for AC and excluded studies that analyzed the risk factors of OM for cervical cancer where the pathologic data of AC was unavailable, such as the studies performed by Yamamoto, Min-Jeong Kim, and Ting Hu, Le Zhou [5,8,10]. A meta-analysis performed by Chen *et al.* [19] believed that stage IIB, deep stromal invasion, corpus uteri invasion and parametrial invasion were risk factors for OM in AC. Our meta-analysis found that IIA was also a risk factor. A systemic review by Touhami concluded that age >45, FIGO >stage IB, deep stromal invasion, lympho-vascular space invasion, corpus invasion, parametrial invasion and tumor size >4 cm were risk factors [28]. Our meta-analysis found that age >45 (OR 0.95, 95% CI 0.46–1.97, $I^2$ = 0%) and tumor grade (OR 0.93,95% CI 0.4–2.18, $I^2$ = 0%) were not the risk factors for OM in early stage AC.

**Table 3. Selection criteria for ovarian preservation in patients with adenocarcinoma of the cervix.**

| Preoperative factors |
|---|
| Desire to preserve the ovaries |
| FIGO ≤IB2 |
| No corpus uteri invasion (CT) |
| No deep stromal invasion (biopsy and cervical conization) |
| Tumor size <4 cm |
| No lympho-vascular space invasion (biopsy and cervical conization) |
| Intraoperative factors |
| Normal ovarian appearance |
| No evidence of extra-uterine spread |

Our meta-analysis determined deep stromal invasion, tumor size >4 cm and lympho-vascular space invasion were risk factor for OM in AC. According to NCCN guidelines, deep stromal invasion, tumor size >4 cm and lympho-vascular space invasion were also intermediate risk factors for pelvic recurrence [29]. Besides FIGO IIB, we also found FIGO IIA a risk factor for OM. Gynecological examination and CT before operation are useful to evaluate vaginal and parametrial involvement.

Finally, we established criteria for ovarian preservation in AC. The preoperative factors were as follows: desire to preserve the ovaries, no corpus uteri invasion (CT), no deep stromal invasion (cervical conization), tumor size <4 cm, FIGO stage ≤IB2 (FIGO 2018), and no lympho-vascular space invasion (biopsy and cervical conization). The intraoperative factors were as follows: normal ovarian appearance and no evidence for extra-uterine spread (Table 3).

Regarding the limitations of this study, we only included retrospective studies. The standard of ovarian preservation for AC needs to be further verified by prospective studies. The overall survival analysis was limited by small numbers. Given it was only limited to stage I disease, it is difficult to make a definitive conclusion.

## 5. Conclusions

Ovarian preservation is only recommended in stage IA and stage IB AC without risk factors, but it is not reasonable for stage IIA and IIB AC. Both stage IIA and IIB are risk factors for OM in early stage AC.

## Author contributions

DW—Investigation, Formal analysis, Resources, Manuscript writing. LZ—Data collection. NB—Supervision, Validation, Manuscript editing. LY—Data collection. YNW—Investigation, Data collection. YCW—Data analysis. MML—Manuscript editing. JL—Manuscript editing. JW—Funding acquisition, Project development. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.


## Acknowledgment

Not applicable.

## Funding

This study was supported by Jiangsu Provincial Medical Talent (2016KJQWZDRC-02).


## Conflict of interest

The authors declare no conflict of interest.

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