Systematic Review and Meta-Analysis

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Ovarian metastasis in women with cervical carcinoma in stages IA to IIB

A systematic review and meta-analysis

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Abstract

Background: Cervical cancer is one of the common malignancies that afflict women worldwide. In rare cases, cervical cancer leads to ovarian metastasis (OM), resulting in poor outcomes. We conducted a systematic review and meta-analysis to evaluate the incidence and risk factors of OM in patients with adenocarcinoma (ADC) or squamous cell carcinoma (SCC) of the cervix.

Methods: We searched articles focused on OM in cervical carcinoma in PubMed, Embase, and the Cochrane Central Register of Controlled Trials. A meta-analysis was performed including selected publications. Pooled odds ratio (OR) and 95% confidence interval (95% CI) were calculated using random-effects models. The heterogeneity was evaluated by the I^2 test. $I^2 > 50\%$ was considered high heterogeneity.

Results: A total of 12 studies with 18,389 patients with cervical cancer in International Federation of Gynecology and Obstetrics stages IA to IIB were included in the meta-analysis. The overall incidence of OM was 3.61% among patients with ADC and 1.46% among patients with SCC (ADC vs SCC: OR 3.89, 95% CI 2.62–5.78; $P < .001$). Risk factors for OM were age >40 years (OR 1.79, 95% CI 1.02–3.13), bulky tumor (OR 2.65, 95% CI 1.77–3.95), pelvic lymph node involvement (PLNI; OR 9.33, 95% CI 6.34–13.73), lymphovascular space involvement (LVSI; OR 4.38, 95% CI 1.86–10.31), parametrial invasion (PMI; OR 7.87, 95% CI 5.01–12.36), and corpus uteri invasion (CUI; OR 7.64, 95% CI 2.51–23.24). PLNI, LVSI, and PMI were the leading risk factors, contributing to OM with respective population attributable fractions of 64.8%, 58.8%, and 51.5%.

Conclusion: The incidence of OM is relatively low in ADC and SCC patients. Risk factors for OM include PLNI, LVSI, PMI, bulky tumor, CUI, or age over 40 years, with the first 3 contributing more to risk of OM.

Abbreviations: ADC = adenocarcinoma, CI = confidence interval, CUI = corpus uteri invasion, DSI = deep stromal invasion, FIGO = International Federation of Gynecology and Obstetrics, LVSI = lymphovascular space involvement, NOS = The Newcastle-Ottawa Quality Assessment Scale, OM = ovarian metastasis, OR = odds ratio, PAF = population attributable fraction, PLNI = pelvic lymph node involvement, PMI = parametrial invasion, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses, SCC = squamous cell carcinoma.

Keywords: cervical carcinoma, meta-analysis, ovarian metastasis, risk factors

1. Introduction

Cervical cancer is the most common gynecologic cancer and the 4th leading cause of cancer-related death in women. According to the World Health Organization, in 2018 approximately 570,000 new cases of cervical cancer were diagnosed and 311,000 deaths occurred due to this malignancy, making it a major health challenge worldwide.[1] The most common histologic types are squamous cell carcinoma (SCC) and adenocarcinoma (ADC), accounting for nearly 75% and 25% of all cervical carcinomas.[2] The diagnosis of cervical cancer at early stages has advanced thanks to the improvement in screening programs, which could provide access to more effective treatments and improved prognosis.[1,3]

Both the US National Comprehensive Cancer Network and the International Federation of Gynecology and Obstetrics (FIGO) recommend hysterectomy with different radicality based on stage, bilateral pelvic lymphadenectomy, and elective oophorectomy for patients with cervical cancer stages IA1 to IIA1.[4,5] Although ovarian metastasis (OM) is not a frequent event in cervical cancer, it decreases patient survival.[6] Nowadays, oophorectomy has been suggested as a primary procedure to

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YF and MW contributed equally to the work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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prevent recurrence in patients with ADC,[7] while ovarian preservation in patients with early stage cervical cancer, especially in SCC, is widely accepted.[8] Oophorectomy in young patients is associated with a high risk of osteoporosis, palpitations, constipation, musculoskeletal disease, and pain due to lack of estrogens.[9] In addition, the incidence of cervical cancer is increasing in young and premenopausal women,[10,11] many of whom express the desire to preserve fertility or at least ovarian function. Thus, whether preservation of the ovaries is reasonable and appropriate for every cervical cancer patient remains controversial.

These considerations highlight the need to identify pathologic and clinical risk factors related to OM in ADC and SCC, which may help gynecologists to decide whether to recommend oophorectomy. Therefore, we conducted a comprehensive systematic review and meta-analysis of available observational studies to identify the incidence and risk factors of OM in patients with ADC and SCC.

2. Methods

This meta-analysis was performed in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement, and was registered with the International Prospective Register of Systematic Reviews (CRD42019133590). The study was approved by the hospital Ethics Committee.

2.1. Literature search

We searched for studies focused on the incidence of OM in SCC or ADC of the cervix in PubMed, Embase, and Cochrane Central Register of Controlled Trials databases from their respective inceptions until March 2019. The predefined search strategy was the following: (cervical cancer OR cervix cancer OR cervical carcinoma OR cervix carcinoma OR cervical neoplasm OR cervix neoplasm) AND (ovarian metastasis OR ovary metastasis OR ovarian metastases OR ovary metastases). Only publications in English were included. There were no limitations regarding publication date, article type, or publication status. We also reviewed the references within the included publications to identify related studies.

2.2. Study selection

Two authors (YF and MYW) independently screened the titles and abstracts to identify relevant studies based on the eligibility criteria. ADC was defined as adenocarcinoma, adenosquamous carcinoma, or mixed type, since the clinical treatments and outcomes are similar.[12] After initial selection, the full texts of all potential articles were independently read by 2 authors (YF and MYW) for further evaluation. Any disagreement was resolved by discussion with the corresponding authors (JKL and AZ).

To be included, studies had to be observational with a prospective cohort, retrospective cohort or case–control design; diagnose OM by pathology; report detailed clinicopathologic risk factors for OM in SCC or ADC; and be available as full text. Studies were excluded if they were case reports, reviews, or systematic reviews; were published in languages other than English; involved samples smaller than 220 patients[13]; failed to report detailed data on OM; or failed to score adequately in the quality assessment (see Section 2.4).

2.3. Data extraction

Two researchers (YF and MYW) independently extracted the following data from each study: name of the first author, publication year, country, inclusion year, primary treatment, number of patients with SCC or ADC, number of patients with OM, and potential risk factors including age, tumor size, pelvic lymph node involvement (PLNI), lymphovascular space involvement (LVSI), parametrial invasion (PMI), deep stromal invasion (DSI), and corpus uteri invasion (CUI). Discrepancies in data extraction were resolved by discussion with the corresponding authors (JKL and AZ).

2.4. Quality assessment

The methodologic quality of the included studies was assessed independently by 2 researchers (YF and MYW) based on the Newcastle-Ottawa Quality Assesment Scale.[14] For the criterion of "Comparability of cohorts on the basis of the design or analysis," studies that controlled for histologic type received one star and studies that further controlled for other factors were assigned two stars. For the criterion of "Assessment of outcome," studies that used microscopic biopsy to diagnose OM received 1 star. For the criterion of "Adequacy of follow up of cohorts," studies with a follow-up rate higher than 85% were assigned 1 star. Studies awarded with 6 or more stars were considered to be of high quality and finally included in our meta-analysis.

2.5. Statistical analysis

Statistical analyses were performed using the meta and metabias packages in STATA 15.0 (Statacorp, College Station, TX). We calculated the odds ratios (ORs) and 95% confidence intervals (CIs) for dichotomous variables collected from all eligible studies. We added 0.5 to every cell in 2×2 tables including zeros, as recommended by the Cochrane Handbook.[15] Heterogeneity was quantified with the I^2 statistic, and $I^2 > 50\%$ was considered high heterogeneity. Random-effects and fixed-effect models give similar results with low heterogeneity, while the random-effects model is more accurate with high heterogeneity. Given the heterogeneity across studies for pooled outcomes (see Section 3), we used a random-effects model and displayed the results of meta-analyses in forest plots. To explore the potential causes of heterogeneity, we used a Galbraith radial plot. We additionally conducted subgroup analyses sorted by publication year, country, and other features. Begg test and Egger test were used to evaluate the presence of publication bias. A P value $<.1$ was considered as evidence of significant publication bias.

Following the recommendation of the World Health Organization, we calculated the population attributable fraction (PAF) of individual risk factors for OM to identify their contributions to overall risk using the formula[16]

$$\mathrm{PAF} = P*(\mathrm{RR}-1)/[1+P*(\mathrm{RR}-1)],$$

where P refers to the proportion of population vulnerable to exposure, which was defined as the rate of risk factors among patients without OM; and RR refers to relative risk, which was calculated using the formula[17]

$$\mathrm{RR} = \mathrm{OR}/(1-P_0+P_0*\mathrm{OR}),$$

where P_0 is the risk of OM in the unexposed group, which was defined as the rate of OM among patients without risk factors we investigated.

3. Results

3.1. Characteristics of the included studies

A flowchart summarizing the process of study selection is shown in Figure 1. The initial search identified 1537 articles, from which 85 duplicate references were removed, and 1428 references were excluded based on the eligibility criteria. From them, 24 full-text studies were screened, of which 12 were included in the final analysis.[6,7,13,18–26] A total of 18,389 patients were included with FIGO stages IA to IIB (FIGO 2009). Among the 12 studies, one was a prospective cohort survey, while the others were retrospective cohort surveys. The geographical regions of the studies were as follows: Japan (n=7), China (n=2), Thailand (n=1), the United States (n=1), and Italy (n=1). The general characteristics of these 12 studies are summarized in Table 1.

3.2. Histologic type and OM

In the 18,389 patients included, the overall incidence of OM was 3.61% (148/4105) in those with ADC and 1.46% (209/14,284) in those with SCC. According to the histologic analysis, compared with SCC, patients with ADC were at higher risk of OM (OR 3.89, 95% CI 2.62–5.78; $P<.001$; $I^2=49.8\%$; Fig. 2A). Since some autopsy samples were included in reference,[26] we removed autopsy samples of this reference and repeated the meta-analysis (OR 4.64, 95% CI 3.14–6.83; $P<.001$; Supplementary Fig. S1, http://links.lww.com/MD/E533). The results were similar to the previous analysis, but the heterogeneity was reduced ($I^2=33.0\%$; $P=.126$).

Because of the moderate heterogeneity in the meta-analysis of OM across all studies ($I^2=49.8\%$; $P=.025$), we performed subgroup analyses sorted by country, the country's income rank (high vs low/middle), early or advanced cancer stage, publication year, and study type. These approaches did not identify clear sources of heterogeneity. A Galbraith radial plot, in contrast, led to the identification of three studies potentially causing heterogeneity[7,22,26] (Supplementary Fig. S2, http://links.lww.com/MD/E534). Furthermore, sensitivity analysis showed that heterogeneity was reduced by excluding reference[26] ($I^2=26.6\%$; $P=0.191$; Supplementary Fig. S3, http://links.lww.com/MD/E535).

3.3. Other risk factors for OM

3.3.1. Age. Two studies[6,23] including a total of 6999 patients evaluated age over 40 years as a risk factor. Therefore we defined

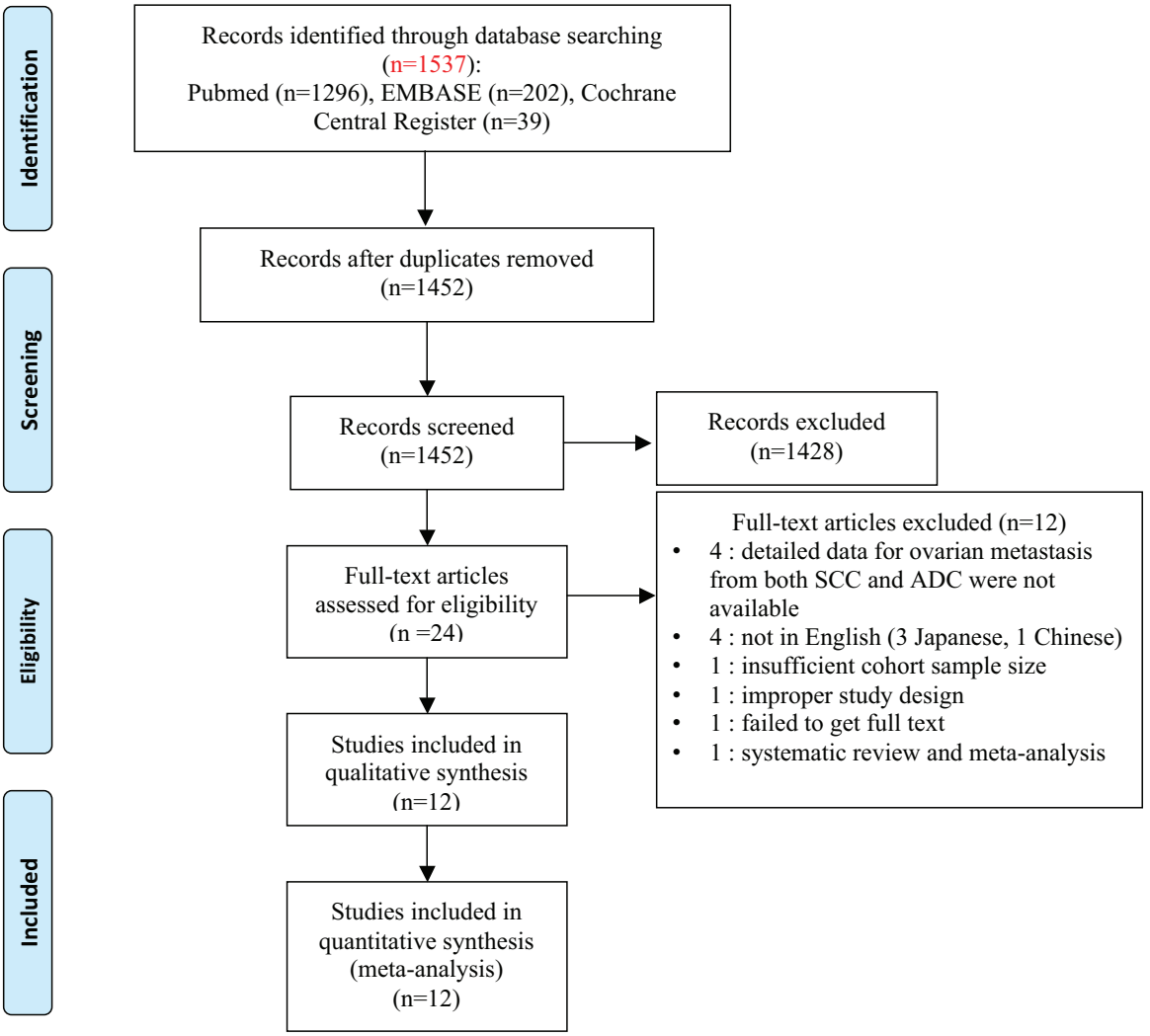

Figure 1. Flow diagram of literature searching and study selection. ADC = adenocarcinoma, SCC = squamous cell carcinoma.

Table 1

Characteristic of each study included in the present meta-analysis.

First author (yr)	Country	Study type	Inclusion year	Cohort size	Tumor stage	Type of tumor				Quality assessment*
						ADC	OM from ADC	SCC	OM from SCC	
Matsuo[6] (2018)	Japan	R	2004–2008	5625	IB–IIB	1915	42	3710	27	7
Xie[19] (2018)	China	R	2003–2015	645	IB–IIA	113	1	532	9	6
Hu[18] (2013)	China	R	2002–2008	1876	IB–IIB	255	9	1621	12	7
Ngamcherttakul[13] (2012)	Thailand	R	2007–2011	182	IA–IIA	14	0	168	1	7
Kasamatsu[20] (2009)	Japan	R	1984–2003	576	IB–IIB	122	6	454	6	8
Landoni[21] (2007)	Italy	R	1982-2004	1664	IA2–IIA	380	9	1284	7	8
Shimada[22] (2006)	Japan	R	1981–2000	3471	IB–IIB	546	29	2925	23	7
Nakanishi[23] (2001)	Japan	R	1974–2000	1304	IA–IIB	240	15	1064	14	7
Yamamoto[7] (2001)	Japan	R	1977–1999	537	IB–IIB	132	7	405	1	6
Sutton[24] (1992)	USA	P	1981–1984	973	IB	203	2	770	4	6
Toki[25] (1990)	Japan	R	1973–1987	591	IB–IIB	67	2	524	1	7
Tabata[26] (1987)	Japan	R	1965–1985	945	IA–IIB	118	26	827	104	8
Total				18389		4105	148	14284	209	

ADC = adenocarcinoma, OM = ovarian metastasis, P = prospective, R = retrospective, SCC = squamous cell carcinom.
* Quality assessment was measured by the Newcastle-Ottawa Quality Assessment Scale.[14]

40 years as a cut-off age. Risk of OM was higher among those older than 40 years (OR 1.79, 95% CI 1.02–3.13, $P = .041$; $I^2 = 0.0\%$; Fig. 2B).

3.3.2. Bulky tumor. Since studies grouped tumors into different size categories, we pooled data using the most common cut-off of 4 cm for FIGO stages IB2 and IIA2. In total, 8880 patients from 3 studies[6,18,21] were included in this analysis. The incidence of OM was 1.93% (54/2802) among patients with bulky tumor (>4 cm) and 0.74% (45/6078) among patients with smaller tumors. Accordingly, OM risk was significantly higher among cervical cancer patients with bulky tumors than among patients with smaller tumors (OR 2.65, 95% CI 1.77–3.95; $P < .001$; $I^2 = 0\%$; Fig. 2C). We were unable to analyze OM risk by stage (IB2 or IIA2) because the included studies did not report separate data by stage.

3.3.3. Pelvic lymph node involvement. Six studies[6,13,18,21,23,26] investigated the relationship between PLNI and OM, one[26] of which we excluded because patients had not been staged IA to IIB. The overall incidence of OM was 4.00% (102/2550) among patients with PLNI and 0.44% (36/8209) among patients without PLNI. Meta-analysis indicated that PLNI increased the risk of OM in cervical cancer (OR 9.33, 95% CI 6.34–13.73; $P < .001$; $I^2 = 0\%$; Fig. 3A).

Only 1 study[6] including 5697 patients presented data on the relationship between para-aortic lymph node metastases and OM, so we did not conduct a meta-analysis.

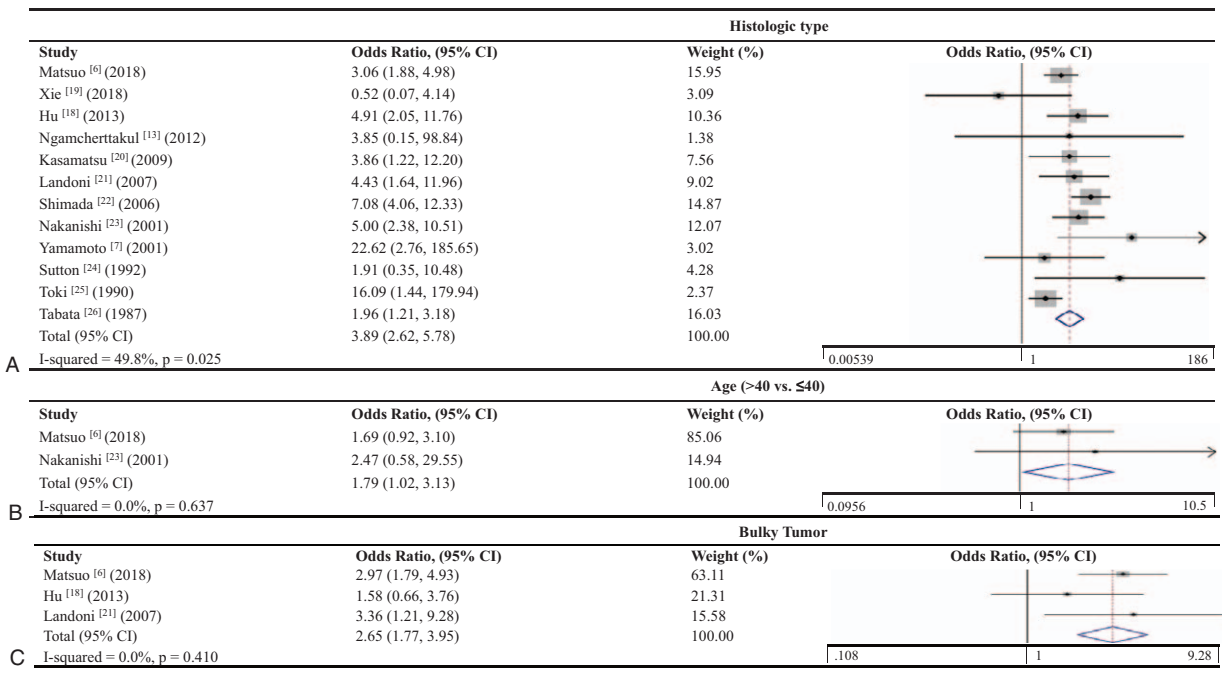

Figure 2. Forest plots of the association between ovarian metastasis in cervical cancer and (A) histologic type of cancer, (B) age (>40 vs ≤40 years), or (C) bulky tumor. All meta-analyses were performed using a random-effects model. CI = confidence interval.

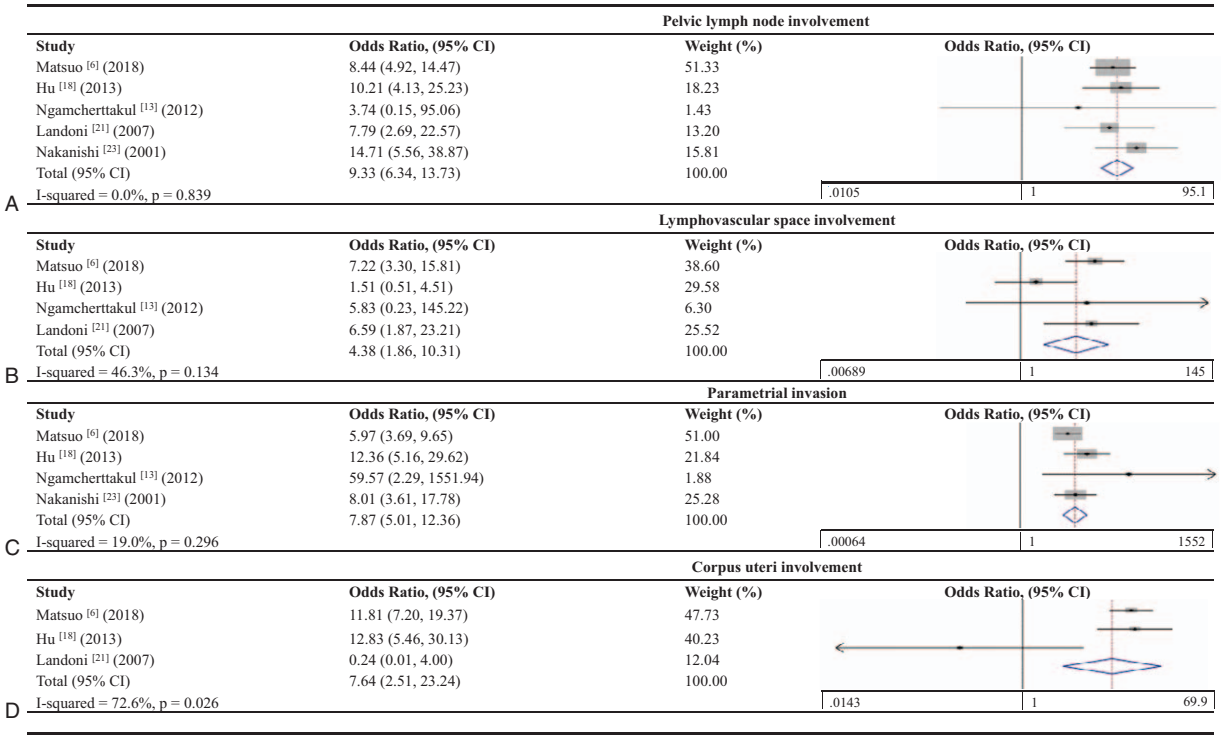

Figure 3. Forest plots of the association between ovarian metastasis in cervical cancer and (A) pelvic lymph node involvement, (B) lymphovascular space involvement, (C) parametrial invasion, or (D) corpus uteri involvement. All meta-analyses were performed using a random-effects model. CI = confidence interval.

3.3.4. Lymphovascular space involvement. Four studies[6,13,18,21] with a total of 9270 patients were included in this analysis. OM was identified in 1.98% (80/4043) of patients with LVSI and in 0.54% (28/5227) of patients without LVSI. The analysis showed that LVSI was a risk factor for OM (OR 4.38, 95% CI 1.86–10.31; $P=0.001$; $I^2=46.3\%$; Fig. 3B).

3.3.5. Parametrial invasion. Four studies[6,13,18,23] including 9107 patients examined the relationship between PMI and OM. A random-effects model showed that the incidence of OM was 4.63% (71/1534) among patients with PMI and 0.67% (51/7573) among patients without PMI. The pooled results confirmed that PMI increased the risk of OM (OR 7.87, 95% CI 5.01–12.36; $P<.001$; $I^2=19.0\%$; Fig. 3C).

3.3.6. Deep stromal invasion. Although we aimed to evaluate the relationship between DSI and OM, quite different criteria for DSI were used in each study, and therefore we were unable to perform a pooled analysis.

3.3.7. Corpus uteri invasion. Three studies[6,18,21] including a total of 9253 patients reported the relationship between CUI and OM. Overall incidence of OM was 5.00% (56/1120) among patients with CUI and 0.64% (52/8133) among patients without CUI, and meta-analysis showed that patients with CUI were at higher risk of OM (OR 7.64, 95% CI 2.51–23.24; $P<0.001$; $I^2=72.6\%$; Fig. 3D).

3.4. Contribution of each risk factor to OM risk

Among the 7 risk factors investigated in our study, we identified PLNI, LVSI, and PMI as the 3 leading risk factors, with respective PAFs of 64.8%, 58.8%, and 51.5% (Table 2).

3.5. Publication bias

Neither the Begg test ($P=.945$) nor visual assessment of funnel plots (Fig. 4) showed any evidence of publication bias.

4. Discussion

In the present meta-analysis, the overall incidence of OM was relatively low, 3.61% in ADC and 1.46% in SCC, in patients with cervical cancer in FIGO stages IA to IIB. The overall incidence of OM was significantly higher in patients with ADC than in SCC (OR 3.89, 95% CI 2.62–5.78; $P<.001$). These results are in agreement with a previous meta-analysis that suggested a higher incidence of OM in early stage ADC than in SCC.[27]

Our meta-analysis also assessed several potential risk factors for OM in cervical cancer. The pooled results indicated that the

Table 2

Population attributable fraction of each risk factor for ovarian metastasis.

Risk factor	Group	Estimated RR	*P*, %	PAF, %
Histologic type	ADC vs SCC	3.73	21.9	37.5
Age	>40 vs ≤40	1.78	74.4	36.7
Bulky tumor	>4 cm vs ≤4cm	2.62	31.3	33.6
PLNI	Involved vs Not	9.00	23.0	64.8
LVSI	Involved vs Not	4.30	43.3	58.8
PMI	Involved vs Not	7.52	16.3	51.5
CUI	Involved vs Not	7.33	11.6	42.4

P refers to the proportion of population vulnerable to exposure, which was defined as the rate of risk factors among patients without OM.

CUI = corpus uteri invasion, LVSI = lymphovascular space involvement, PAF = population attributable fraction, PLNI = pelvic lymph node involvement, PMI = parametrial invasion, RR = relative risk.

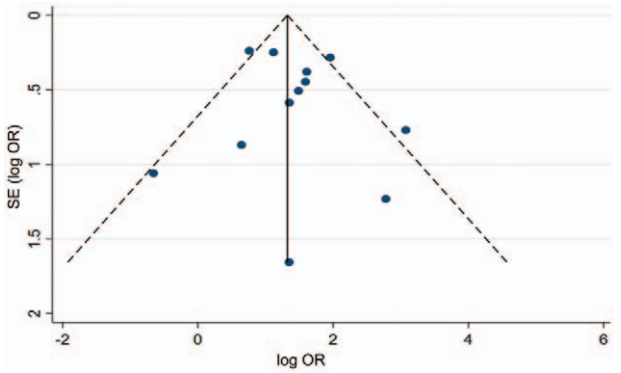

Figure 4. Funnel plot of the 12 included studies with pseudo 95% confidence limits. OR = odds ratio, SE = standard error.

risk of OM was higher in patients with older age (>40 years) (OR 1.79, 95% CI 1.02–3.13), bulky tumor (OR 2.65, 95% CI 1.77–3.95), PLNI (OR 9.33, 95% CI 6.34–13.73), LVSI (OR 4.38, 95% CI 1.86–10.31), PMI (OR 7.87, 95% CI 5.01–12.36), or CUI (OR 7.64, 95% CI 2.51–23.24). Our results are consistent with a previous meta-analysis that showed increased risk of OM in SCC patients with suspicious PLNI, CUI, or PMI, as well as in ADC patients with bulky tumor, suspicious CUI, or PMI.[18]

Whether to perform oophorectomy or preserve ovaries and the impact of this decision on survival and recurrence in cervical cancer patients continue to be discussed.[28] Studies[29,30] reported that ADC patients with preserved ovarian functions showed a short-term survival rate similar to that of patients who underwent oophorectomy. We think that a possible reason is that the incidence of OM is relatively low, so it has a limited effect on the overall survival rate in a typical patient cohort. In the long term, according to the Nurses Health Study,[31] patients over 50 years of age who undergo oophorectomy have a higher prevalence of cardiovascular diseases, which constitutes the main cause of death among women worldwide.[32] Moreover, women who undergo oophorectomy and do not receive estrogen therapy are at higher risk of all-cause mortality.[31] Although long-term estrogen therapy may reduce these risks to some extent, it increases the risk of breast cancer.[33] Moreover, while hormone replacement therapy is thought to be safe in patients with SCC, whether it is safe for patients with ADC remains uncertain because of the difference in pathology.[34]

Our results suggest that ovarian preservation may still be safe in young ADC patients.[18,27] However, risk factors for OM, including older age, bulky tumor, PLNI, LVSI, PMI, and CUI should be carefully taken into consideration. Furthermore, we suggest that ovarian function not be preserved in patients who receive postoperative abdominal radiotherapy, since such treatment has been shown to damage ovarian function during 5-year follow-up.[7]

Our meta-analysis presents several limitations. First, our study might have a selection bias since the majority of the included studies are retrospective. Second, the relationship between DSI and OM could not be analyzed due to the use of different definitions and criteria in each study. Third, the pooled results are based on only 12 or fewer studies. This shortcoming was due to the relatively few studies that have analyzed risk factors associated with OM in cervical cancer. Forth, we observed high heterogeneity in the CUI analysis and moderate heterogeneity in the histologic type analysis. We tried to identify sources of heterogeneity through subgroup analyses and Galbraith radial plots. In the end, we identified 1 study[26] that was mainly responsible for the heterogeneity, probably because it analyzed autopsies rather than patients. Finally, since detailed data of each patient could not be obtained, we could only conduct a bivariate analysis of contributions with PAF, while the multivariate analysis could not be conducted in the study.

Despite these limitations, our study still presents important strengths. To our knowledge, the present study is the largest meta-analysis, including 12 studies with 18,389 patients, that explores several clinicopathologic variables as potential risk factors for OM in cervical cancer. This information may help gynecologists to better select the appropriate therapeutic management. All combined results presented low statistical heterogeneity, with the exception of the high heterogeneity of the CUI analysis and the moderate heterogeneity of the histologic type analysis. In these meta-analyses, we applied random-effects models to acquire more reliable results.

In conclusion, the incidence of OM was relatively low in ADC and SCC patients, being nearly 3-fold higher in those with ADC than in those with SCC. Risk factors for OM included older age, bulky tumor, PLNI, PMI, and CUI. These results suggest that ovary preservation might be reasonable and appropriate in young ADC and SCC patients, but special precaution should be taken in patients with older age (>40 years), bulky tumor (>4 cm) or CUI, particularly those with PLNI, LVSI, or PMI.

Author contributions

Conceptualization: Meng-yao Wang, Yu Fan, Jin-ke Li.
Data curation: Yu Fan, Meng-yao Wang, Si-ping Mo.
Formal analysis: Yu Fan, Meng-yao Wang.
Investigation: Yu Fan, Meng-yao Wang.
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Project administration: Jin-ke Li, Ai Zheng.
Software: Yu Fan, Meng-yao Wang.
Supervision: Jin-ke Li, Ai Zheng.
Writing – original draft: Yu Fan, Meng-yao Wang.
Writing – review & editing: Jin-ke Li, Ai Zheng.

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