Ovarian metastasis in women with cervical carcinoma in stages IA to IIB
A systematic review and meta-analysis

Yu Fan, PhD,a,b, Meng-yao Wang, PhD,a,b, Yi Mu, PhD,a, Si-ping Mo, PhD,a,b, Ai Zheng, PhD,a,*,
Jin-ke Li, PhD,a,

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 I² test. I² > 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 2.62–5.89; 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%, 38.8%, 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.[1,2] The most common histologic types are squamous cell carcinoma (SCC) and adenocarcinoma (ADC), accounting for nearly 75% and 25% of all cervical carcinomas.[2,3] 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.[1,4,5]

Both the US National Comprehensive Cancer Network and the International Federation of Gynecology and Obstetrics (FIGO) recommend hysterectomy with different radicability based on stage, bilateral pelvic lymphadenectomy, and elective oophorectomy for patients with cervical cancer stages IA1 to IA1.[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
prevent recurrence in patients with ADC,\textsuperscript{[7]} while ovarian preservation in patients with early stage cervical cancer, especially in SCC, is widely accepted.\textsuperscript{[8]} Oophorectomy in young patients is associated with a high risk of osteoporosis, palpitations, constipation, musculoskeletal disease, and pain due to lack of estrogens.\textsuperscript{[9]} In addition, the incidence of cervical palpitations, constipation, musculoskeletal disease, and pain especially in SCC, is widely accepted.\textsuperscript{[8]} Oophorectomy in young preservation in patients with early stage cervical cancer, discussion with the corresponding authors (JKL and AZ).

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.\textsuperscript{[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;\textsuperscript{[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 (JDKL 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 Assessment Scale.\textsuperscript{[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 $2 \times 2$ tables including zeros, as recommended by the Cochrane Handbook.\textsuperscript{[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\textsuperscript{[16]}

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

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\textsuperscript{[17]}

$$\text{RR} = \text{OR}/(1 - P_0 + P_0\times\text{OR}),$$

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. 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; I² = 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 (I² = 33.0%; P = .126).

Because of the moderate heterogeneity in the meta-analysis of OM across all studies (I² = 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] (I² = 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...
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; I² = 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 4.00% (45/1126) among patients with bulky tumors (≥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; I² = 0.0%; 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; I² = 0.0%; 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.

### Table 1
Characteristics of each study included in the present meta-analysis.

| First author (yr) | Country | Study type | Inclusion year | Cohort size | Tumor stage | ADC | OM from ADC | SCC | OM from SCC | Quality assessment |
|-------------------|---------|------------|----------------|-------------|-------------|-----|-------------|-----|-------------|-------------------|
| Matsuo[6] (2018)  | Japan   | R          | 2004–2008      | 5625        | IB–IB      | 1915 | 42          | 3710 | 27          | 7                 |
| Xie[10] (2018)    | China   | R          | 2003–2015      | 645         | IB–IA      | 113  | 1           | 532  | 9           | 6                 |
| Hu[12] (2013)     | China   | R          | 2002–2008      | 1876        | IB–IB      | 255  | 9           | 1621 | 12          | 7                 |
| Yamamoto[7] (2001)| Japan   | R          | 2007–2011      | 182         | IA–IA      | 14   | 0           | 168  | 1           | 7                 |
| Kasamatsu[10] (2009)| Japan  | R          | 1984–2004      | 576         | IB–IB      | 122  | 6           | 454  | 6           | 8                 |
| Landoni[21] (2007)| Italy   | R          | 1982–2004      | 1664        | IA2–IA4    | 380  | 9           | 1284 | 7           | 8                 |
| Shinimaru[12] (2006)| Japan  | R          | 1981–2000      | 3471        | IB–IB      | 546  | 29          | 2925 | 23          | 7                 |
| Nakahashi[11] (2001)| Japan  | R          | 1974–2000      | 1304        | IA–IB      | 240  | 15          | 1064 | 14          | 7                 |
| Yamamoto[6] (2001)| Japan   | R          | 1977–1990      | 537         | IB–IB      | 132  | 7           | 405  | 1           | 6                 |
| Suto[14] (1992)   | USA     | P          | 1981–1984      | 973         | IB         | 203  | 2           | 770  | 4           | 6                 |
| Toki[15] (1990)   | Japan   | R          | 1973–1987      | 591         | IB–IB      | 67   | 2           | 524  | 1           | 7                 |
| Tabata[16] (1987) | Japan   | R          | 1965–1985      | 945         | IA–IB      | 118  | 26          | 827  | 104         | 8                 |
| Total             |         |            |                | 18389       |            | 4105 | 14          | 14284| 209         |                   |

ADC = adenocarcinoma, OM = ovarian metastasis, P = prospective, R = retrospective, SCC = squamous cell carcinoma.

* Quality assessment was measured by the Newcastle-Ottawa Quality Assessment Scale.[14]

---

**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.
Four studies\cite{6,13,18,23} including 3,3.5. Parametrial invasion.

higher risk of OM (OR 7.64, 95% CI 2.51–23.24; \( P < 0.001 \); \( I^2 = 72.6\% \); Fig. 3D).

3.3.4. Lymphovascular space involvement. Four studies\cite{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 1.51–11.6; \( P = 0.0064 \); \( I^2 = 46.3\% \); Fig. 3B).

3.3.5. Parametrial invasion. Four studies\cite{6,13,18,21} including 9107 patients examined the relationship between PMI and OM. A random-effects model showed that the 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.\cite{27}

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\cite{6,18,21} including a total of 9233 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.\cite{27}

Our meta-analysis also assessed several potential risk factors for OM in cervical cancer. The pooled results indicated that the
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.[18,27] However, risk factors for OM, including older age, bulky tumor, PLNI, LVSI, PMI, and CUI, 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 ovarian function after a transposition. Gynecol Oncol 1958;75:590–600.

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 ovarian function 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[32] 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.
Methodology: Yu Fan, Yi Mu, Si-ping Mo.
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.

References

[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
[2] Small WJ, Bacon MA, Bajaj A, et al. Cervical cancer: a global health crisis. Cancer 2017;123:2404–12.
[3] Serrano R, Brotons M, Bosch FX, et al. Epidemiology and burden of HPV-related disease. Best Pract Res Clin Obstet Gynaecol 2018;47:14–26.
[4] Koh WJ, Abu-Rustum NR, Bean S, et al. Cervical cancer, version 3.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2019;17:64–84.
[5] Bhutla N, Denny L. FIGO Cancer Report 2018. Int J Gynecol Obstet 2018;143(Suppl 2):2–3.
[6] Matsuoka K, Shimada M, Yamaguchi S, et al. Identifying a candidate population for ovarian conservation in young women with clinical stage IB-IIIB cervical cancer. Int J Cancer 2018;142:1022–32.
[7] Yamamoto R, Okamoto K, Yukiharu T, et al. A study of risk factors for ovarian metastases in stage Ib-IIib cervical carcinoma and analysis of ovarian function after a transposition. Gynecol Oncol 2001;82:312–6.
[8] McGill ML, Keaty EC, Thompson JD. Conservation of ovarian tissue in the treatment of carcinoma of the cervix with radical surgery. Am J Obstet Gynecol 1958;75:590–600.
[9] Michelsen TM, Dorum A, Dahl AA. A controlled study of mental distress and somatic complaints after risk-reducing salpingo-oophorectomy in women at risk for hereditary breast ovarian cancer. Gynecol Oncol 2009;113:128–33.

[10] Kokawa K, Takekida S, Kamiura S, et al. The incidence, treatment and prognosis of cervical carcinoma in young women: a retrospective analysis of 4975 cases in Japan. Eur J Gynaecol Oncol 2010;31:37–43.

[11] Smith HO, Tiffany MF, Qualls CR, et al. The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States—a 24-year population-based study. Gynecol Oncol 2000;78:97–103.

[12] Lee JY, Lee C, Hahn SK, et al. A comparison of adenosquamous carcinoma and adenocarcinoma of the cervix after radical hysterectomy. Gynecol Obstet Invest 2015;80:15–20.

[13] Ngamcherttakul V, Ruengkhachorn I. Ovarian metastasis and other ovarian neoplasms in women with cervical cancer stage Ia-IIA. Asian Pac J Cancer Prev 2012;13:4525–9.

[14] Wells G, Shea B, O’Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ontario, Canada: The Ottawa Hospital Foundation; 2014. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed May 3, 2019

[15] Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org. Accessed May 1, 2019

[16] World Health Organization, Health statistics and information systems. Metrics: population attributable fraction (PAF). Available at: https://www.who.int/healthinfo/global_burden_disease/metrics_paf/en/. Accessed March 7, 2020

[17] Wang Z. Converting odds ratio to relative risk in cohort studies with partial data information. J Stat Soft 2013;55.

[18] Hu T, Wu L, Xing H, et al. Development of criteria for ovarian preservation in cervical cancer patients treated with radical surgery with or without neoadjuvant chemotherapy: a multicenter retrospective study and meta-analysis. Ann Surg Oncol 2013;20:881–90.

[19] Xie X, Song K, Cui B, et al. A comparison of the prognosis between adenocarcinoma and squamous cell carcinoma in stage IB-IIA cervical cancer. Int J Clin Oncol 2018;23:522–31.

[20] Kasamatsu T, Onda T, Sowada M, et al. Radical hysterectomy for FIGO stage IIB adenocarcinoma of the uterine cervix. Br J Cancer 2009;100:1400–5.

[21] Landoni F, Zanagnolo V, Lovato-Diaz L, et al. Ovarian metastases in early-stage cervical cancer (Ia2-IIa): a multicenter retrospective study of 1965 patients (a Cooperative Task Force study). Int J Gynecol Cancer 2007;17:623–8.

[22] Shimada M, Kigawa J, Nishimura R, et al. Ovarian metastasis in carcinoma of the uterine cervix. Gynecol Oncol 2006;101:234–7.

[23] Nakanishi T, Wakis K, Ishikawa H, et al. A comparison of ovarian metastasis between squamous cell carcinoma and adenocarcinoma of the uterine cervix. Gynecol Oncol 2001;82:504–9.

[24] Sutton GP, Bundy BN, Delgado G, et al. Ovarian metastases in stage IB carcinoma of the cervix: a Gynecologic Oncology Group study. Am J Obstet Gynecol 1992;166(Prt 1):50–3.

[25] Toki N, Tsukamoto N, Kaku T, et al. Microscopic ovarian metastasis of the uterine cervical cancer. Gynecol Oncol 1991;41:46–51.

[26] Tabata M, Ichinoe K, Sakuragi N, et al. Incidence of ovarian metastasis in patients with cancer of the uterine cervix. Gynecol Oncol 1987;28:255–61.

[27] Jiao XB, Hu J, Zhu LR. The safety of ovarian preservation in early-stage adenocarcinoma compared with squamous cell carcinoma of uterine cervix: a systematic review and meta-analysis of observational studies. Int J Gynecol Cancer 2016;26:1510–4.

[28] Jacoby VL. Hysterectomy controversies: ovarian and cervical preservation. Clin Obstet Gynecol 2014;57:95–105.

[29] Hu J, Jiao X, Yang Z, et al. Should ovaries be removed or not in early-stage cervical adenocarcinoma: a retrospective study of 105 patients. J Obstet Gynaecol 2017;37:1065–9.

[30] Chen J, Wang R, Zhang B, et al. Safety of ovarian preservation in women with stage I and II cervical adenocarcinoma: a retrospective study and meta-analysis. Am J Obstet Gynecol 2016;215:460.e1–3.

[31] Parker WH, Feskanich D, Broder MS, et al. Long-term mortality associated with oophorectomy compared with ovarian conservation in the nurses’ health study. Obstet Gynecol 2013;121:709–16.

[32] World Health Organization, Top 10 causes of death, 2018. Available at: https://www.who.int/gho/mortality_burden_disease/causes_death/top_10/en/. Accessed May 3, 2019

[33] Moch LS, Skovlund CW, Hannafor PD, et al. Contemporary hormonal contraception and the risk of breast cancer. N Engl J Med 2017;377:2228–39.

[34] Deli T, Orosz M, Jakab A. Hormone replacement therapy in cancer survivors - review of the literature. Pathol Oncol Res 2019;26:63–78.