Microsatellite instability leads to poor prognosis in patients with early-stage endometrial cancer? a meta-analysis

Jingping Xiao
The Third Hospital of Mianyang, Sichuan Mental Health Center

Jisheng Wang
The Third Hospital of Mianyang, Sichuan Mental Health Center

Yuanyu Zhao
Sichuan Science City Hospital

Miaoquan He
The Third Hospital of Mianyang, Sichuan Mental Health Center

Jiang Du
Sichuan Science City Hospital

Yunzi Wang ( wangyunzi1104@163.com )
Sichuan Science City Hospital  https://orcid.org/0000-0003-0087-6988

Research article

Keywords: Endometrial cancer, Early-stage, Microsatellite instability, Prognosis, Meta-analysis

DOI: https://doi.org/10.21203/rs.3.rs-132471/v1

License: © This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

Background
Poor prognosis of early-stage endometrial cancer (EC) is often accompanied by microsatellite instability (MSI). We hypothesized that MSI is an independent marker for poor prognosis of early-stage EC. To demonstrate this hypothesis, we evaluated the correlation between MSI and early-stage EC prognosis by meta-analysis.

Methods
Databases such as PubMed, EMBASE and the Cochrane Cooperative Library were searched from inception to October 2020, respectively. The disease-free survival (DFS), the overall survival (OS), and the progression-free survival (PFS) were pooled to analyze the correlation between MSI and prognosis in patients with early-stage EC. Besides, Egger's regression and Begg's test were used to detect Publication bias.

Results
There were 7 studies met the inclusion criteria and were enrolled in our meta-analysis with a sample size of 1150, and the included patients with early-stage EC were all endometrioid endometrial cancer (EEC). The pooled hazard ratios (HRs) in early-stage EC shows that MSI is significantly associated with lower DFS $[HR = 3.90, 95\% CI (2.81–6.99), p = 0.000]$, OS $[HR = 1.48, 95\% CI (1.12–1.96), p = 0.006]$, and PFS $[HR = 2.41, 95\% CI (1.05–5.52), p = 0.038]$. There was no significant heterogeneity in the studies pooled analysis of DFS, OS, and PFS. There was also no statistical publication bias, the $P$-value of Egger’s test of OS and DFS is $p = 0.535$ and $p = 0.639$ respectively.

Conclusion
MSI is most likely an independent marker of poor prognosis in early-stage EC, and this correlation is even more significant in patients with EEC.

Background
Endometrial cancer (EC) is one of the most common cancers in the female reproductive tract, and the increase of incidence and mortality has an up-trend year by year [1, 2]. Assessment of prognosis is of great significance in the clinical management of EC, and prognostic assessment is key to identifying prognostic markers.[3, 4].

Mismatch repair (MMR) contains four proteins: MLH1, MSH2, MSH6 and PMS2. When one or more of these proteins are not expressed, it is called mismatch repair deficiency (MMRd). Due to MMRd, errors produced by DNA replication cannot be repaired in time, known as microsatellite instability (MSI) [5]. MSI is the most sensitive and specific marker of MMRd, and MMRd can be inferred by examining MSI [6, 7].

MSI accounts for 20–40% of patients with sporadic EC and has been associated with endometrioid histology [8, 9]. MSI is considered to be an important prognostic marker in the EC. Therefore, an increasing number of studies have focused on the correlation between MSI and prognosis of EC.

Some studies have shown MSI to be associated with better prognosis in EC [10, 11], some studies have shown the opposite [12–14], and others have shown no correlation with prognosis, including a meta-analysis [15–17]. The same contradiction also exists in studies with early-stage EC [18, 19]. Since patients with early-stage EC usually do not require adjuvant therapy after surgery, MSI is more strongly correlated with prognosis. However, none of the relevant meta-analyses have been reported.

To clarify the correlation between MSI and prognosis of EC, we performed a meta-analysis that included the disease-free survival (DFS), the overall survival (OS), and the progression-free survival (PFS) of early-stage EC.

Methods
Data sources and search strategy
This meta-analysis was rigorously evaluated by the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guideline [20]. Database as PubMed, EMBASE, and the Cochrane Collaboration Library was searched from inception to October 2020, the language restriction was English.

We adjusted the MeSH terms combined with related text words to comply with the relevant rules for searching our interesting studies in each database. Our search strategy was that: (Endometrial Neoplasm or Endometrial Neoplasms or Endometrial Carcinoma or Endometrial Carcinomas or Endometrial Cancer or Endometrial Cancers or Endometrial Neoplasm or Endometrial Neoplasms or Endometrial Carcinoma or Endometrial Carcinomas or Endometrial Cancer or Endometrial Cancers or Endometrium Cancer or Carcinoma of Endometrium Carcinoma or Endometrium Carcinoma or Endometrium Carcinomas or Cancer of Endometrium or Endometrium Cancers) AND (Mismatch repair or Microsatellite Instability or Replication Error Phenotype or Replication Error Phenotypes) AND survival.

Study selection
Two independent researchers (Jing-ping Xiao and Yun-zi Wang) filtered all the titles and abstracts of the retrieved studies to identify potential studies. The retrieved studies that met the inclusion criteria were evaluated in full text. Each of these discrepancies was resolved through discussion, and if conflicts remained, a third reviewer (Ji-sheng Wang) was involved.

Inclusion criteria

Studies containing the correlation between MSI or MMRd and prognosis of EC were included if they met the following criteria. (1) The stage of EC was early (stage I-II); (2) Reported DFS, OS, or PFS associated with MSI or MMRd; (3) Studies directly reported hazard ratios (HRs) with 95% confidence intervals (CIs) or have a Kaplan-Meier survival curves that can be used to extract HRs.

Editorials, meeting reports and letters to the editors were all excluded.

Data extraction

Two researchers independently screened articles following inclusion criteria, and any differences were resolved by consensus. From each study, we extracted study characteristics, baseline characteristics, and pre-established outcomes for DFS, OS, and PFS.

Quality Assessment

Two researchers (Jing-ping Xiao and Yun-zi Wang) separately applied the Newcastle-Ottawa Statement to evaluate the quality of eligible studies, including selection, comparability, and exposure. Nine points were included in the scale, and a score greater than or equal to 7 was considered to be a high-quality study. A score of 4-6 was considered a good quality study and a score of 3 or less was considered a low-quality study [21], and discrepancies were resolved through discussion, with the involvement of a third reviewer (Ji-sheng Wang) if a conflict remained.

Data synthesis and analysis

A Stata (version 14) software was used to analyze all results. The hazard ratios (HRs) would be extracted and calculated by the Kaplan-Meier survival curves if there was not a directly available HRs in the study. If an $I^2$ greater than or equal to 50% indicated significant heterogeneity, the HRs were merged with the corresponding 95% CIs using a random-effects model; otherwise, the fixed-effects model was used. Publication bias was statistically assessed by Egger's regression and Begg's test, where a $p$-value < 0.05 was considered to be a significant publication bias.

Results

Literature search

Figure 1 illustrates the flow of the selection of eligible articles. A total of 720 articles were identified by searching PubMed, Cochrane, and EMBASE. 469 articles remained after removing duplicate files. Following the scanning of titles and abstracts, 50 articles were selected for full-text reading. Finally, we included seven studies [18, 19, 22-26] that met the inclusion criteria for our meta-analysis.

Study characteristics

Table 1 shows the characteristics of the seven studies included. Of these studies, four studies were conducted in Europe (Spain, Italy, and Norway) [18, 19, 22, 23], one study was conducted in Asia (Korea) [25], two studies were conducted in the Americas (Canada) [24, 26]. Five studies directly reported HRs for DFS, OS, or PFS, while HRs of the other two studies [18, 25] were extracted from Kaplan-Meier survival curves. Seven studies were cohort studies and one study was a clinical trial. Four studies assessed MSI by using five recommended quasimonomorphicmononucleotide markers, and three studies assessed MSI by immunohistochemistry testing. As shown in Table 2, all studies scored 7 or higher and were high-quality studies.

Correlation between MSI and DFS in early-stage EC

The pooled HRs in early-stage EC shows that MSI is significantly associated with lower DFS [HR=3.90, 95%CI (2.81-6.99), $p=0.000$], as shown in Figure 2a. Meanwhile, there was not a heterogeneity about DFS ($I^2=0.0\%$, $p=0.583$).

Correlation between MSI and OS in early-stage EC

The pooled HRs in early-stage EC shows that MSI is significantly associated with lower OS [HR=1.48, 95%CI (1.12-1.96), $p=0.006$], as shown in Figure 2b. Meanwhile, there was not a significant heterogeneity about OS ($I^2=25.9\%$, $p=0.256$).

Correlation between MSI and PFS in early-stage EC

As shown in Figure 2c, the pooled HRs in early-stage EC shows that MSI is significantly associated with lower PFS [HR=2.41, 95%CI (1.05-5.52), $p=0.038$]. Meanwhile, there was not a heterogeneity about PFS ($I^2=0.0\%$, $p=0.607$).

Publication bias

No significant publication bias was detected by the funnel plot test (Figure 3). Additionally, there was also no statistical publication bias, the $p$-values of Egger’s test for DFS and OS are $p=0.639$ and $p=0.535$ respectively.
Sensitivity analysis

To explore the sensitivity of the pooled HRs of DFS, OS, and PFS in early EC, we omitted each study individually from the pooled analysis. The exclusion of any study had no significant influence on the results (Figure 4).

Discussion

The correlation between MSI and EC prognosis has been one of the hot topics of studies for more than two decades. Unfortunately, most of the current studies on the correlation between MSI and prognosis of EC have shown inconsistent results. For example, the meta-analysis by Diaz-Padilla et al. showed no correlation between MSI and prognosis in patients with EC [15], Nagle et al. reported that MSI was significantly associated with poor prognosis [27], while Black et al. showed that MSI was significantly associated with a good prognosis [10]. Therefore, the clinical prognostic significance of MSI in EC remains unclear.

By this meta-analysis, we found that a significant association between MSI and poorer prognosis in early-stage EC. We analyzed the correlation between MSI and prognosis of early-stage EC by DFS, OS, and PFS, then found that the DFS, OS, and PFS of early-stage EC patients with MSS (microsatellite stability) were significantly higher than patients with MSI, which is consistent with the cancer-specific survival of early-stage EC reported in the study by Bilbao et al. [23]. Also, none of the three pooled forest plots were heterogeneous, so we used a fixed-effects model, which proved the high reliability of the results we obtained.

Furthermore, in the study by Black et al. [10], MSI was associated with a good prognosis for EC, which is the opposite of our findings. The reason for the analysis maybe that 20% of the patients included in Black's study were non-endometrioid endometrial cancer (EEC). In contrast, in our meta-analysis, the included patients with early-stage EC were all EEC, which may indicate that MSI can be significantly associated with worse prognosis only in EEC patients, which is also consistent with the study by Nagle et al. [27].

Usually, the majority of patients with EC in all clinical stages (stages I-IV) received one or more adjuvant therapies, which increase the uncertainty as to whether MSI has a prognostic predictive role. Whereas, in our study, women with early-stage EC generally did not receive adjuvant therapy after surgery. Thus, our study is better able to exclude the confounding effects of adjuvant therapy and illustrate the correlation between MSI and EC.

There are still some deficiencies in our study. First, some of the data came from the extraction of survival curves, which may produce some deviations compared with the real data. Second, the number of studies included in the pooled PFS was small, and more studies are needed to support our conclusions. Third, the vast majority of the studies we included were retrospective case studies, which carries the risk of selective reporting. Fourth, the four studies used genotyping for MSI detection, and other three of the included studies used immunohistochemistry for MSI detection, but so far, the concordance between the two detection methods has not been ascertained in EC.

Conclusions

The results of our meta-analysis showed that MSI is most likely an independent marker of poor prognosis in early-stage EC, and this correlation is even more significant in patients with EEC. This correlation requires more large-scale, well-designed prospective studies as well as randomized controlled trials to illustrate the mechanisms of the relationship between MSI and early EC.

Abbreviations

EC  Endometrial cancer
MSI  Microsatellite instability
DFS  Disease-free survival
OS  Overall survival
PFS  Progression-free survival
MMR  Mismatch repair
MMRd  Mismatch repair deficiency
PRISMA  Preferred Reporting Items for Systemic Reviews and Meta-Analyses
CIs  Confidence intervals
Acknowledgments

With thanks to all participants in this study and the Bethune Medical Science Research Foundation.

Author contributions

JPX and YZW designed the study and wrote the manuscript. YYZ and JD developed the search strategy and completed the literature search. JSW and MQH developed the inclusion and exclusion criteria for the eligible studies. JPX, YZW, and JSW reviewed the eligible studies and extracted the data. JPX, YZW, and MQH did the methodological judgement. YYZ and JD performed the statistical analysis methods. JPX, YZW, and JD summarized the original data. Contributions to the interpretation of the data and review of the manuscript were made by all authors. All authors have read and approved the manuscript.

Funding

This work was supported by the Bethune Medical Science Research Foundation (SCZ007CS). However, the funder had no role in the design, conduct or analysis of this study, or the decision to submit results.

Availability of data and materials

Meta-analysis is a secondary analysis, which the data are all fully available without restriction, and all the material can be found in the included original studies.

Consent for publication

Not applicable.

Conflict of interest

The authors declare that they have no conflict of interest.

Compliance with ethical standards

No ethical approval or formal consent is required for this type of study.

References

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2020. CA: a cancer journal for clinicians 2020, 70(1):7-30.
2. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2019. CA: a cancer journal for clinicians 2019, 69(1):7-34.
3. Kim SR, Pina A, Albert A, McAlpine J, Wolber R, Blake Gilks C, Kwon JS: Does MMR status in endometrial cancer influence response to adjuvant therapy? Gynecologic oncology 2018, 151(1):76-81.
4. Reijnen C, Kusters-Vandevelde HVN, Prinsen CF, Massuger L, Snijders M, Kommoos S, Brucker SY, Kwon JS, McAlpine JN, Pijnenborg JMA: Mismatch repair deficiency as a predictive marker for response to adjuvant radiotherapy in endometrial cancer. Gynecologic oncology 2019, 154(1):124-130.
5. Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, Meltzer SJ, Rodriguez-Bigas MA, Fodde R, Ranzani GN et al: A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer research 1998, 58(22):5248-5257.
6. Nelson GS, Pink A, Lee S, Han C, Morris D, Ogilvie T, Duggan MA, Kobel M: MMR deficiency is common in high-grade endometrioid carcinomas and is associated with an unfavorable outcome. Gynecologic oncology 2013, 131(2):309-314.
7. Joehlin-Price AS, Perrino CM, Stephens J, Backes FJ, Goodfellow PJ, Cohn DE, Suarez AA: Mismatch repair protein expression in 1049 endometrial carcinomas, associations with body mass index, and other clinicopathologic variables. Gynecologic oncology 2014, 133(1):43-47.
8. MacDonald ND, Salvesen HB, Ryan A, Iversen OE, Akslen LA, Jacobs IJ: Frequency and prognostic impact of microsatellite instability in a large population-based study of endometrial carcinomas. Cancer research 2000, 60(6):1750-1752.
9. Gordhandas S, Kahn RM, Gamble C, Talukdar N, Maddy B, Nelson BB, Askin G, Christos PJ, Holcomb K, Caputo TA et al: Clinicopathologic features of endometrial cancer with mismatch repair deficiency. Ecancermedicalscience 2020, 14:1061.
10. Black D, Soslow RA, Levine DA, Tomos C, Chen SC, Hummer AJ, Bogomolniy F, Olvera N, Barakat RR, Boyd J: Clinicopathologic significance of defective DNA mismatch repair in endometrial carcinoma. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2006, 24(11):1745-1753.
11. Kato M, Takano M, Miyamoto M, Sasaki N, Goto T, Tsuda H, Furuya K: DNA mismatch repair-related protein loss as a prognostic factor in endometrial cancers. Journal of gynecologic oncology 2015, 26(1):40-45.
12. McMeekin DS, Tritchler DL, Cohn DE, Mutch DG, Lankes HA, Geller MA, Powell MA, Backes FJ, Landrum LM, Zaino R et al: Clinicopathologic Significance of Mismatch Repair Defects in Endometrial Cancer: An NRG Oncology/Gynecologic Oncology Group Study. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2016, 34(25):3062-3068.
13. Nout RA, Bosse T, Creutzberg CL, Jurgenliemk-Schulz IM, Jobson JJ, Lutgens LC, van der Steen-Banasik EM, van Eijk R, Ter Haar NT, Smit VT: Improved risk assessment of endometrial cancer by combined analysis of MSI, PI3K-AKT, Wnt/beta-catenin and P53 pathway activation. Gynecologic oncology 2012, 126(3):466-473.
14. Shih KK, Garg K, Levine DA, Kauff ND, Abu-Rustum NR, Soslow RA, Barakat RR: Clinicopathologic significance of DNA mismatch repair protein defects and endometrial cancer in women 40 years of age and younger. *Gynecologic oncology* 2011, 123(1):88-94.

15. Diaz-Padilla I, Romero N, Amir E, Matias-Guiu X, Villar E, Muggia F, Garcia-Donas J:Mismatch repair status and clinical outcome in endometrial cancer: a systematic review and meta-analysis. *Critical reviews in oncology/hematology* 2013, 88(1):154-167.

16. Arabi H, Guan H, Kumar S, Cote M, Bandyopadhyay S, Bryant C, Shah J, Abdul-Karim FW, Munkarah AR, Ali-Fehmi R: Impact of microsatellite instability (MSI) on survival in high grade endometrial carcinoma. *Gynecologic oncology* 2009, 113(2):153-158.

17. Zighelboim I, Goodfellow PJ, Gao F, Gibb RK, Powell MA, Rader JS, Mutch DG: Microsatellite instability and epigenetic inactivation of MLH1 and outcome of patients with endometrial carcinomas of the endometrioid type. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2007, 25(15):2042-2048.

18. Ruiz I, Martin-Arruti M, Lopez-Lopez E, Garcia-Orad A: Lack of association between deficient mismatch repair expression and outcome in endometrial carcinomas of the endometrioid type. *Gynecologic oncology* 2014, 134(1):20-23.

19. Steinbakk A, Malpica A, Slew A, Skaland I, Gudlaugsson E, Janssen EA, Lovslett K, Fiane B, Kruse AJ, Feng W et al: Biomarkers and microsatellite instability analysis of curettings can predict the behavior of FIGO stage I endometrial endometrioid adenocarcinoma. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology,* Inc 2011, 24(9):1262-1271.

20. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of clinical epidemiology* 2009, 62(10):1006-1012.

21. Stang A: Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European journal of epidemiology* 2010, 25(9):603-605.

22. Fiumicino S, Ercoli A, Ferrandina G, Hess P, Raspaglio G, Genuardi M, Rovella V, Bellacosa A, Cicchillitti L, Mancuso S et al: Microsatellite instability is an independent indicator of recurrence in sporadic stage III endometrial adenocarcinoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2001, 19(4):1008-1014.

23. Bilbao C, Lara PC, Ramirez R, Henriquez-Hernandez LA, Rodriguez G, Falcon O, Leon L, Peruro M, Diaz-Chico BN, Diaz-Chico JC: Microsatellite instability predicts clinical outcome in radiation-treated endometrioid endometrial cancer. *International journal of radiation oncology, biology, physics* 2010, 76(1):9-13.

24. Mackay HJ, Gallinger S, Tsao MS, McLachlin CM, Tu D, Keiser K, Eisenhauer EA, Oza AM: Prognostic value of microsatellite instability (MSI) and PTEN expression in women with endometrial cancer: results from studies of the NCIC Clinical Trials Group (NCIC CTG). *European journal of cancer (Oxford, England : 1990)* 2010, 46(8):1365-1373.

25. Kim J, Kong JK, Yang W, Cho H, Chay DB, Lee BH, Cho SJ, Hong S, Kim JH: DNA Mismatch Repair Protein Immunohistochemistry and MLH1 Promoter Methylation Testing for Practical Molecular Classification and the Prediction of Prognosis in Endometrial Cancer. *Cancers* 2018, 10(9).

26. Kim SR, Pina A, Albert B, McAlpine JN, Wolber R, Gilks B, Carey MS, Kwon JS: Mismatch repair deficiency and prognostic significance in patients with low-risk endometrioid endometrial cancers. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society* 2020, 30(6):783-788.

27. Nagle CM, O’Mara TA, Tan Y, Buchanan DD, Obermair A, Blomfield P, Quinn MA, Webb PM, Spurdle AB, Australian Endometrial Cancer Study G: Endometrial cancer risk and survival by tumor MMR status. *Journal of gynecologic oncology* 2018, 29(3):e39.

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

| Author          | Year | Number of patients | Stage distribution | histology | Microsatellite markers | Microsatellite instability definition | Outcome assessment | Study design     |
|-----------------|------|--------------------|--------------------|-----------|------------------------|----------------------------------------|---------------------|------------------|
| Kim et al.      | 2020 | 475                | IA                 | EEC       | MLH1, MSH2, MSH6, PMS2 | ≥1 of 4 MMR protein was lost            | OS/PFS              | Cohort study     |
| Kim et al.      | 2018 | 151                | I-I                | EEC       | MLH1, MSH2, MSH6, PMS2 | ≥1 of 4 MMR protein was lost            | OS/PFS              | Cohort study     |
| Ruiz et al.     | 2014 | 163                | I-I                | EEC       | MLH1, MSH2, MSH6, PMS2 | ≥1 of 4 MMR protein was lost            | OS/DFS              | Cohort study     |
| Steinbakk et al.| 2011 | 171                | I                  | EEC       | BAT26, BAT25, NR-21, NR-24, NR-27 | ≥2 of 5 markers with mutant alleles | OS                  | Cohort study     |
| Bilbao et al.   | 2010 | 93                 | I-I                | EEC       | BAT26, BAT25, NR-21, NR-24, NR-27 | ≥2 of 5 markers with mutant alleles | DFS                 | Cohort study     |
| Mackey et al.   | 2010 | 97                 | I-I                | EEC       | BAT26, BAT25            | ≥1 of 2 markers with mutant alleles      | DFS                 | Clinical Trials  |
| Fiumicino et al.| 2001 | 65                 | I-I                | EEC       | D2S123, D2S119, D9S171, D9S157, D10S216, BAT26 | ≥2 of 6 markers with mutant alleles | DFS                 | Cohort study     |

EEC: endometrioid endometrial cancers; MMR: mismatch repair; OS: overall survival; PFS: progression-free survival; DFS: disease-free survival; NR: not reported.

**Table 2** Methodological quality of cohort studies included in the meta-analysis.

| Authors         | Year | Representativeness of the exposed cohort | Selection of the unexposed cohort | Ascertainment of exposure | Outcome of interest not present at start of study | Control for important factor or additional factor | Outcome assessment | Follow up long enough for outcomes to occur | Adequacy of follow up of cohorts | Total quality scores |
|-----------------|------|-----------------------------------------|----------------------------------|---------------------------|---------------------------------------------------|-------------------------------------------------|---------------------|------------------------------------------|---------------------------------|----------------------|
| Kim et al.      | 2020 | +*                                      | +                                | +                         | +                                                 | +                                               | +                   | +                                        | +                               | 8                    |
| Kim et al.      | 2018 | +                                       | +                                | +                         | ++                                                | +                                               | +                   | +                                        | +                               | 9                    |
| Ruiz et al.     | 2014 | +                                       | +                                | +                         | ++                                                | +                                               | -                   | .**                                      | +                               | 8                    |
| Steinbakk et al.| 2011 | +                                       | +                                | +                         | -                                                 | +                                               | +                   | +                                        | +                               | 7                    |
| Bilbao et al.   | 2010 | +                                       | +                                | +                         | ++                                                | +                                               | -                   | +                                        | +                               | 8                    |
| Mackey et al.   | 2010 | +                                       | +                                | +                         | ++                                                | +                                               | +                   | +                                        | +                               | 8                    |
| Fiumicino et al.| 2001 | +                                       | +                                | +                         | +                                                 | +                                               | +                   | +                                        | +                               | 9                    |

* If there is a positive symbol that means score one point; ** A negative symbol means no point.

**Figures**
720 articles identified through database searching
Pubmed (n=251), Embase (n=444), Cochrane Library (n=25)

Duplicates (n=251)

Studies viewed for eligibility through title and abstracts (n=469)

Unrelated studies excluded (n=373)
Meeting reports (n=46)

Studies assessed for eligibility through full text (n=50)

Non-carily endometrial carcinoma (n=41)
Clinical outcome cannot be judged (n=1)
HR cannot be pooled (n=1)

Included studies in this meta-analysis (n=7)

Figure 1
The flow diagram of studies included in this meta-analysis.