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The association between statin use and endometrial cancer survival outcome

A meta-analysis

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Abstract

Background: Previous studies on the association between statin use and survival outcomes in gynecologic cancers have presented conflicting results. No independent studies to elucidate the association between statin use and survival outcomes of endometrial cancer (EC) have been conducted.

Methods: To gather updated evidence, we carried out an extensive literature search on Medline (PubMed and OvidSP), Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), wanfang data, and Vip network to identify all potential studies on the effect of statins on the prognosis of endometrial carcinoma. The design and quality of all studies were evaluated, and a fixed-effects model was used to calculate pooled hazard ratios (HRs) for overall survival (OS) and disease-specific survival (DSS).

Results: Of the 219 articles screened, 9 articles were eligible, including 8 articles and 1 abstract. A total of 5923 patients with endometrial cancer who used statins were identified. Statin use was related to increased overall survival (HR, 0.80; 95% confidence interval [CI], 0.66–0.95, without significant heterogeneity, $I^2=52\%$, $P=.080$). Statin users also had increased disease-specific survival (HR, 0.69; 95% CI, 0.61–0.79, $I^2=0.0\%$).

Conclusion: Statins are beneficial to the survival outcome of patients with endometrial cancer. The selection of statins as a 1st-line agent seems justified for endometrial carcinoma.

Abbreviations: CI = confidence interval, CNKI = China National Knowledge Infrastructure, DSS = disease-specific survival, EC = endometrial cancer, HR = hazard ratios, NOS = Newcastle–Ottawa Scale, OS = overall survival, PFS = progression-free survival, RFS = recurrence-free survival.

Keywords: endometrial cancer, meta-analysis, statin, survival outcomes

1. Introduction

Endometrial cancer (EC) is the 7th most common malignant disease in the world and is the most common gynecologic malignancy in developed countries.[1] The incidence has increased year by year, with 54,870 new cases were diagnosed in the United States in 2015.[2] Women with a long or excessive exposure to estrogen have a remarkably increased risk of EC.[3] Most of the women with EC (75%) are diagnosed at an early stage, and their 5-year survival rate is relatively high. However, the prognosis of patients in the advanced stage is still poor.[4] There is still room for improvement, especially regarding the selection of adjuvant therapy.[3,5] Many of the established medications with known anticancer functions, such as statins,[6] aspirin,[7] metformin, vitamin D,[8] and bisphosphonates,[9] have been deemed as adjuvant anticancer therapies, which can improve prognosis. Statins are widely used to reduce plasma cholesterol which prevents cardiovascular diseases. An increasing number of studies have proved that using statins may increase the survival outcome of gynecologic cancer, although the current results are still controversial.

Statins inhibit the 3-hydroxy-3-methylglutaryl coenzyme A reductase, which can reduce cholesterol and triglyceride and reversibly inhibit the conversion of 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate.[10] Lowered cholesterol and systemic anti-inflammatory effects are the mechanisms by which statins decrease the incidence of cancer and subsequent death.[11,12] Preclinical evidence suggests that statins can inhibit the proliferation, invasion, and metastasis of tumor cells.[13–15] However, the results regarding survival outcomes remain controversial. Nevadunsky et al indicated that statin users had higher disease-free survival rates than nonusers.[16] However, Goodman et al found that the survival of patients with EC who used statins after hysterectomy was not statistically significant.[17] In light of these conflicting findings, we performed a meta-analysis of observational studies to determine whether the use of statins is associated with improvements in the survival rate of patients with EC. As far as we know, our meta-analysis is the 1st independent study concerning the relationship between statin use and the survival of patients with EC.

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Table 1

Characteristics of the 7 included studies.

Author	Publication	Location	Study type	Number of patients (Observed/ exposure)	Survival analysis	Follow-up time, y	NOS score	Matched/adjusted variables*
Sanni[32]	2017	UK	Cohort study.	3646/1134	DSS	6.1	8	1; 2; 3; 4; 5
Nevadunsky[16]	2015	USA	Retrospective cohort study	983/220	DSS	3.28	4	NR
Wang[33]	2016	USA	Prospective cohort study	14632/704	DSS	14.6	7	14; 15; 16; 17; 18; 19
Yoon[34]	2015	USA	Retrospective cohort study	2987/1893	OS	NR	8	1; 2; 3; 6; 7;20; 21; 22; 23; 24; 25; 26; 27; 28
Feng[35]	2016	USA	Retrospective cohort study	199/50	OS,PFS	2.58	6	1; 2; 4;6; 7; 8;30; 31; 27; 28; 29;32; 33; 34;
Lavie[36]	2013	Israel	Case–control	274/45	OS	0.43	7	1
ARIMA[37]	2018	Austria	Cohort study.	105/43	OS	4.6	5	NR
Dyg Sperling[38]	2108	Denmark.	cohort study.	6694/1208	DSS	4.5	8	1;2;5;9;22;30;37–40
Arsdale[39]	2017	USA	retrospective cohort study	NR/621	DSS	2.04	0	1; 4; 6; 7; 27; 28;35, 32; 36; 30

DSS = disease-specific survival, OS = overall survival, PFS = progression-free survival, NR = not report, NOS = Newcastle-Ottawa scale.

* 1, Age at diagnosis; 2, tumber stage; 3, tumber grade; 4, BMI; 5, year of diagnosis; 6, race; 7, diabetes; 8, smoking history; 9, education; 10, physical activity; 11, family history of cancer; 12, current health-care provider; 13, oral contraception use; 14, prior unopposed oestrogen use; 15, prior oestrogen plus progestin use; 16, solar irradiance (latitude); 17, prior CHD history; 18, age at menarche; 19, randomization into the CaD trial; 20, neighborhood income; 21, hysterectomy type; 22, chemotherapy; 23, radiation; 24, Charlson score; 25, impaired glucose tolerance; 26, obesity; 27, dyslipidemia; 28, hypertension; 29, parity; 30, histology subtype; 31, lymph node involvement; 32, aspirin use; 33, treatment modality; 34, use of nonstatin lipid-lowering medications; 35, metformin use; 36, antihypertensive medications; 37, disposable income, 38, marital status, 39, co-morbidity, 40, concomitant drug use.

2. Materials and methods

2.1. Retrieval strategy

The content of this meta-analysis strictly follows the PRISMA checklist for reporting. We searched databases (PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure, wanfang data, and Vip network) for all articles and abstracts that were published from their inception to July 10, 2018, and assessed the association between statins and outcomes in patients with EC. No restrictions on language or type of publication were imposed. Our overall search strategy included terms for endometrial neoplasms (e.g., "Neoplasm, Endometrial," "Endometrial Carcinoma," "Endometrial Cancer,", and "Endometrium Cancer") and statins (e.g., "Hydroxymethylglutaryl-CoA Reductase Inhibitors," "Inhibitors, Hydroxymethylglutaryl-CoA Reductase," "Reductase Inhibitors, Hydroxymethylglutaryl-CoA," and "Inhibitors, HMG-CoA Reductase"). We also searched the references of the included articles to expand the range of data retrieval and improve the recall rate.

2.2. Selection criteria and exclusion criteria

Two authors independently reviewed all retrieved studies, removed duplicate records and screened the titles and abstracts. A detailed assessment of potential related references was carried out to determine their qualifications. Any differences between them were discussed with a third reviewer (Sun). The searched articles were included in the meta-analysis if they met the following criteria:

1. Studies that assessed the relationship between statin use and survival outcome in endometrial cancer;
2. Nonrandomized studies that used an epidemiologic study design (case control or cohort study);
3. Studies that presented the hazard ratio (HR) and 95% confidence interval (CI) or data needed for their calculation;
4. Studies that evaluated disease-specific survival (DSS), overall survival (OS), progression-free survival (PFS) or recurrence-free survival (RFS);
5. Studies that were published most recently, if there were studies involving the same population and the same author that were published repeatedly.

Articles were excluded if they met the following criteria:

1. Reviews, editorials, case reports, or letters to the editor or
2. Studies that reported the risk relationship between statins use and EC.

2.3. Data extraction and quality assessment

The full texts of articles that met the inclusion criteria were obtained. Two reviewers (Li and Liu) are independently extracted the data and evaluated the quality of the obtained documents. They sought to obtain information from the literature, including information regarding author(s), publication year, region, study type, follow-up time, patients, statin exposure, survival analysis, and matched/adjusted variables. Detailed information is shown in Table 1. If multiple estimates of effect (HR) were reported in the same article, we chose the estimate obtained after multivariable adjustment. When the HR and 95% CI were not available, we extracted original data from the article to calculate them. We mainly extracted the HR of OS, DSS and type II DSS. Since all eligible studies were observational studies, the Newcastle–Ottawa Scale (NOS) was used to assess their quality. The NOS utilizes three broad perspectives to assess a study which are the selection of groups, comparability of groups and exposure or outcome of individual observational studies. The specific score is calculated as follows: 1 star represents 1 point, and a short span represents 0 points. Data extraction and quality assessment were carried out independently by 2 reviewers (Li and Liu), who consulted with the 3rd reviewer (Sun) in case of any disagreement.

2.4. Statistical analysis

The HR and related statistical data were extracted directly from the included literature or calculated using a published method. The specific method used is as follows: if both the observed (O)

Table 2

Quality scores of included studies using Newcastle-Ottawa scale (NOS).

Study	Representativeness of exposed group	Representativeness of non-exposed group	Record of exposure factor	Not observed outcome at first	Matched and/or adjusted factors	Evaluation of outcome	Enough follow-up time	Loss to follow-up <20%	Overall Score
Sanni[32]	★	★	★	★	★★	★	★	–	8
Nevadunsky[16]	★	★	★	–	–	★	–	–	4
Wang[33]	★	★	★	★	★★	★	★	–	7
Yoon[34]	★	★	★	★	★★	★	★	–	8
Feng[35]	★	★	★	–	★	★	★	–	6
ARIMA[37]	★	–	★	★	–	★	★	–	5
Dyg Sperling[38]	★	★	★	★	★★	★	★	–	8
Arsdale[39]									

Study	Definition of a clear case	Representative of the case	The choice of control	Definition of control	Comparability of cases and controls	Confirm the exposure	Exposure to comparability	No response rate	Overall Score
Lavie[36]	★	★	★	★	★	★	★	–	7

★ represented 1 point; -represented 0 point.

and predicted (E) events in the study and control groups are presented in the trial report, HR can be directly calculated as the risk rate ratio:

$$\mathrm{HR} = \left[\frac{\text{Observed events research}/log\text{ rank expected events research}}{\text{Observed events control}/log\text{ rank expected events control}}\right]$$

The HRs[18] in each qualified study were merged to form a pooled HR. Q test (assessing the P-value) and I^2 tests were used to evaluate the degree of heterogeneity in eligible studies. When $P < .10$ or $I^2 > 50\%$, which represented significant heterogeneity, we chose a random effect model. If $P > .10$, a fixed effect model was chosen. We explored the effects of statin use on OS and DSS in patients with EC. Since the prognosis of II EC is poor, we performed a separate analysis for it. To assess the robustness of the aggregated outcome of overall survival and disease-specific survival, we conducted a sensitivity analysis by omitting any single study to determine the source of instability. If the number of studies incorporated into the meta-analysis was greater than 10 ($N > 10$), we created funnel plots to assess publication bias.[19] The analysis was performed using Stata version 12.0 software (Stata Corporation, College Station, TX). In addition, it is worth mentioning that all analyses were based on previous published studies, thus no ethical approval and patient consent are performed.

3. Results

3.1. Literature search

In the initial search, 21 articles on statin use and EC outcomes were available for further review after the titles and abstracts of 219 papers were screened. Among the 21 articles investigating the effect of statins on the prognosis of endometrial cancer, 6 were excluded for not reporting the survival rate of patients with EC,[20–25] and 3 were excluded for lack of useful data.[26–28] Two abstracts[29,30] and 1 meta-analysis[31] were also excluded. Ultimately, 8 articles and 1 abstract were included in the meta-analysis.

3.2. Description of studies and quality assessment

Our analysis included a total of nine observational studies, involving more than 30,141 participants, 5923 of whom were patients with EC who took statins. Eight studies were cohort studies,[16,32–35,37–39] and 1 study was a case–control study.[36] Five articles studied the relationship between the use of statins and the disease-specific survival of endometrial cancer,[16,32,33,38,39] 3 articles discussed the overall survival,[34,36,37] and 1 article considered the overall survival and progression-free survival.[35] One of these studies was published in the form of an abstract.[39] Most of them were published from 2013 to 2017, with 5 studies in the United States,[16,33–35,39] 1 study in Britain,[32] 1 in Austria,[37] 1 in Denmark[38] and another 1 in Israel.[36] Most individual studies had matched or adjusted variables, including age at diagnosis, tumor stage, tumor grade, BMI, year of diagnosis, race, diabetes status, and smoking history. Characteristics of all the studies are summarized in Table 1.

The NOS scores ranged from 4 to 8, where high-quality studies were deemed to be those studies that had 6 awarded stars. High-quality studies included 5 cohort studies[32–35,38] and 1 case–control study.[36] The quality scores of these studies are summarized in Table 2.

3.3. Meta-analysis

The 9 studies included 12 sets of data because three studies reported 2 sets of available data. The 12 sets of data reported the HR and 95% confidence intervals of the effect on statin use in EC on the overall survival (OS) and disease-specific survival (DSS). The results of four studies investigating the correlation between statins and DSS in patients with EC indicated that the use of statins was related to an improved DSS (HR, 0.69; 95% CI, 0.61–0.79) (Fig. 1). The corresponding I^2 was 0.0%, and there was no heterogeneity. We conducted an analysis based on cancer type, although only 3 studies reported the DSS of type II endometrial cancer. The results of these three studies indicated that statin use was related to an improvement in DSS (HR 0.64; 95% CI, 0.50–0.81) (Fig. 2), with a corresponding I^2 of 0.0%. As only one study was a prospective cohort study,[33] we performed a subgroup analysis based on the type of study design to clarify its impact on the outcome (Fig. 3). It was found that the results of the retrospective cohort study were HR = 0.69, 95% CI (0.60–0.79). And this prospective study did not result in a qualitative change in the overall outcome. We also

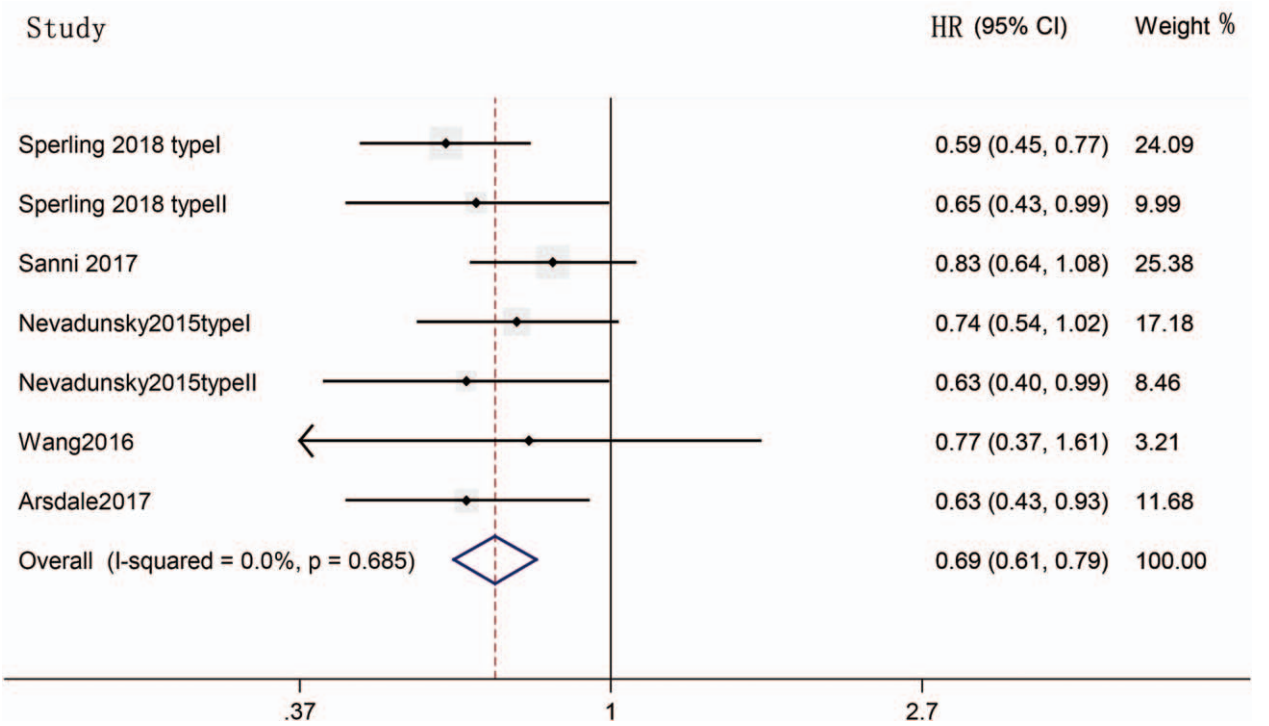

Figure 1. A forest map of the relationship between the use of statins and disease-specific survival (DSS) in patients with endometrial cancer (EC).

evaluated the relationship between the use of statins and the OS of patients with EC. The results proved that the OS was improved, though the supporting evidence had some limitations (HR, 0.80; 95% CI, 0.66–0.95) (Fig. 4). PFS in endometrial cancer was not analyzed because only one set of data reported this measure.[35] The sensitivity analysis results were stable, and no single study qualitatively changed the pooled HRs. The results of the meta-analysis on the impact of statin on the OS and DSS of patients with EC were not changed by excluding any single study per iteration. For example, after excluding 1 study (Lavie 2013), the use of statin continued to be related to improved OS (HR 0.88, 95% CI 0.72–1.07). Similarly, after exclusion of the abstract (Arsdale 2017), the use of statin continued to be associated with improved DSS (HR 0.69, 95% CI 0.61–0.80). Details are shown in Figures 5 and 6. Although only 9 studies were included, we still created funnel plots to assess publication bias. The results showed no significant publication bias. Details are shown in Figure 7.

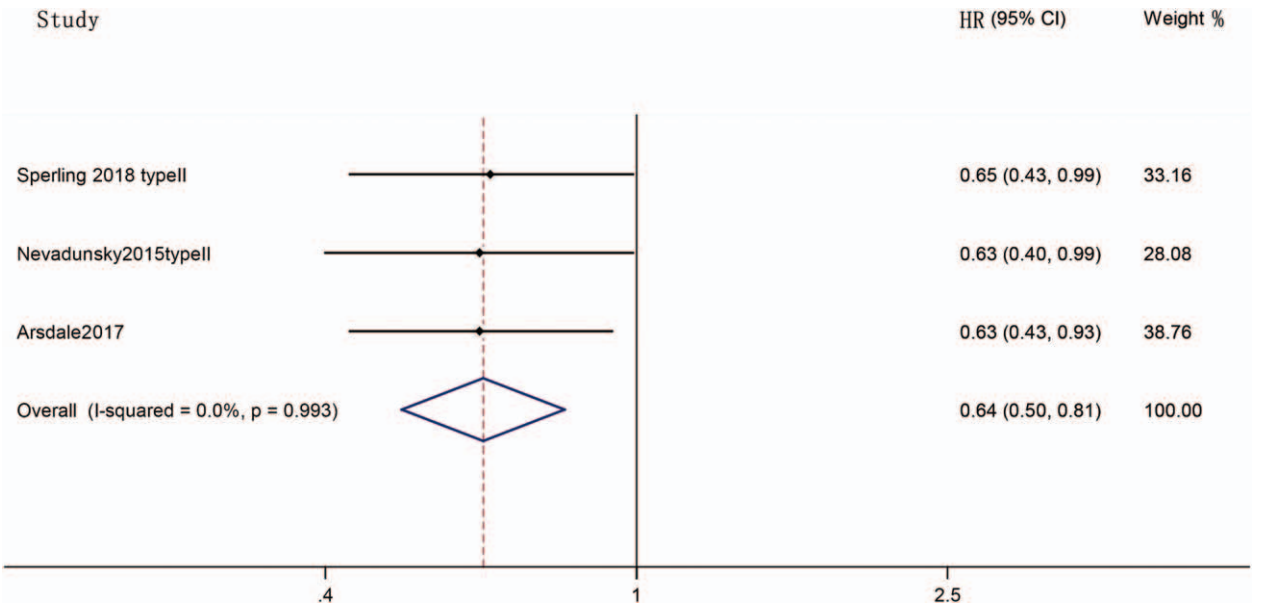

Figure 2. A forest map of the relationship between the use of statins and disease-specific survival (DSS) in type II patients with endometrial cancer (EC).

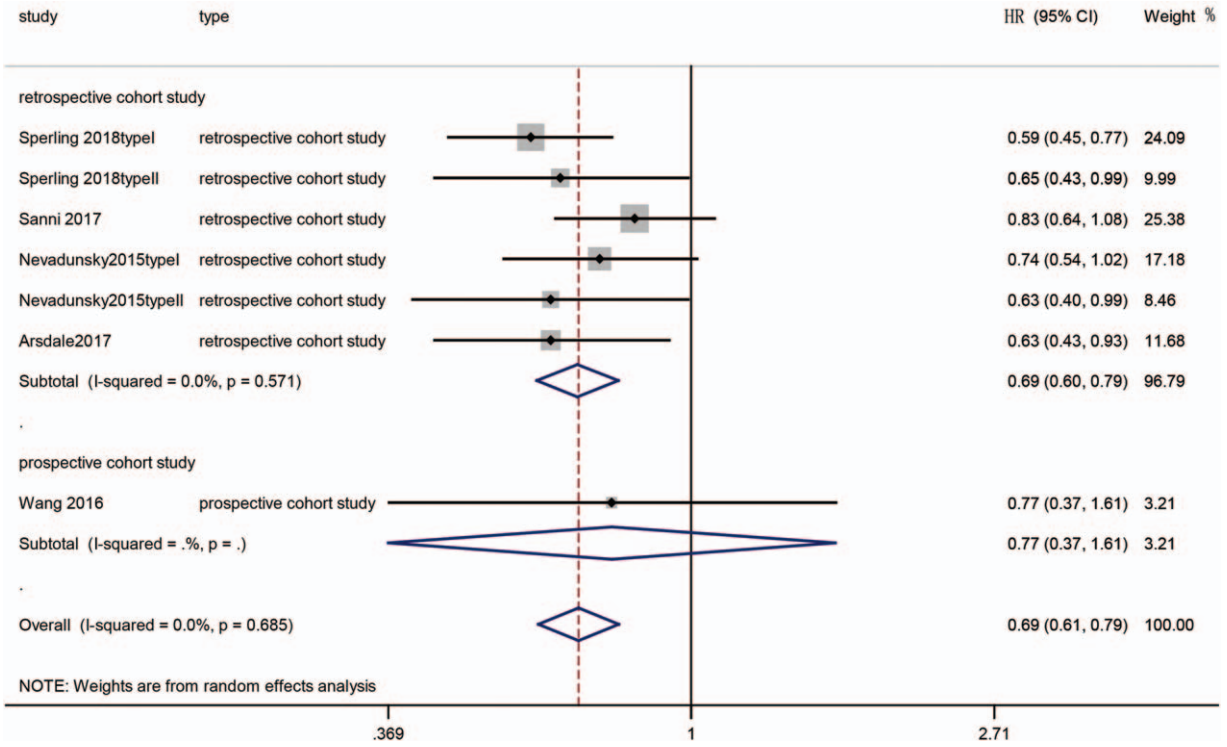

Figure 3. A subgroup analysis of the risk relationship between the use of statins and disease-specific survival (DSS) in patients with endometrial cancer (EC) based on the type of study design.

4. Discussion

The impact of using statins on the survival of patients with endometrial cancer (EC) is of great significance in guiding the clinical practice of oncologists. Based on seven observational studies that provided objective evidence on the use of statins, the present meta-analysis indicates that statin use may increase the survival of patients with EC. In particular, it can prolong the DSS of patients with EC, although the evidence had some limitations.

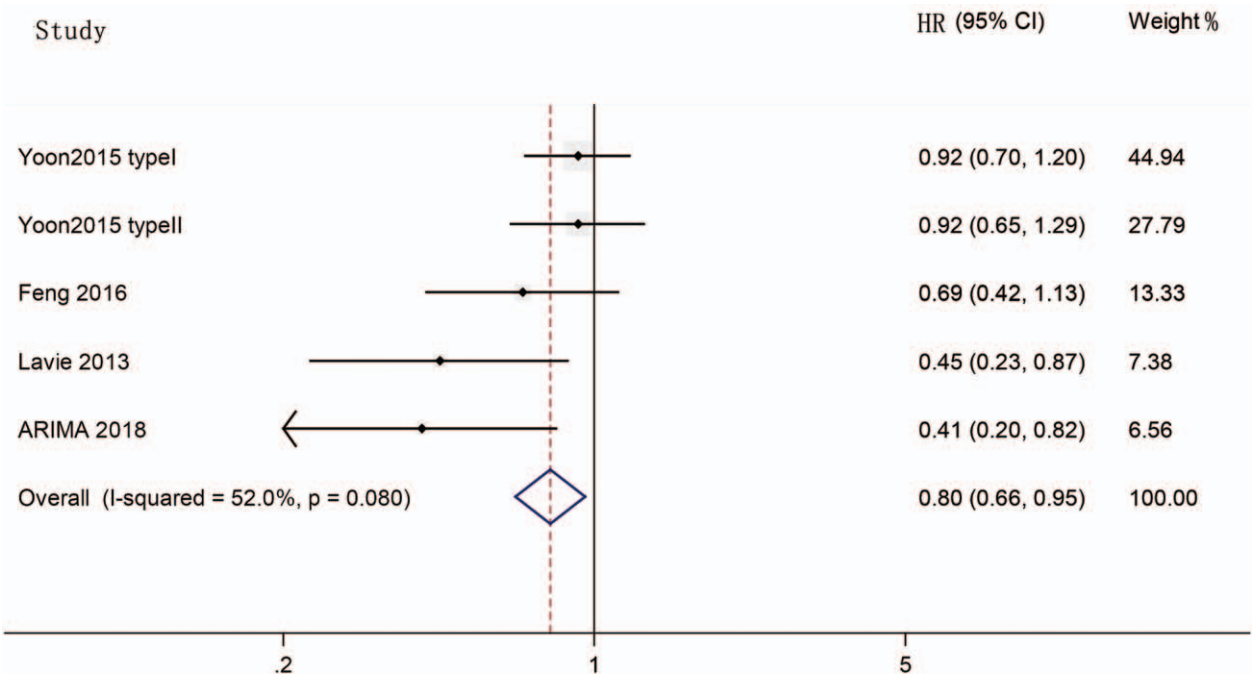

Figure 4. A forest map of the relationship between the use of statins and overall survival (OS) in patients with endometrial cancer (EC).

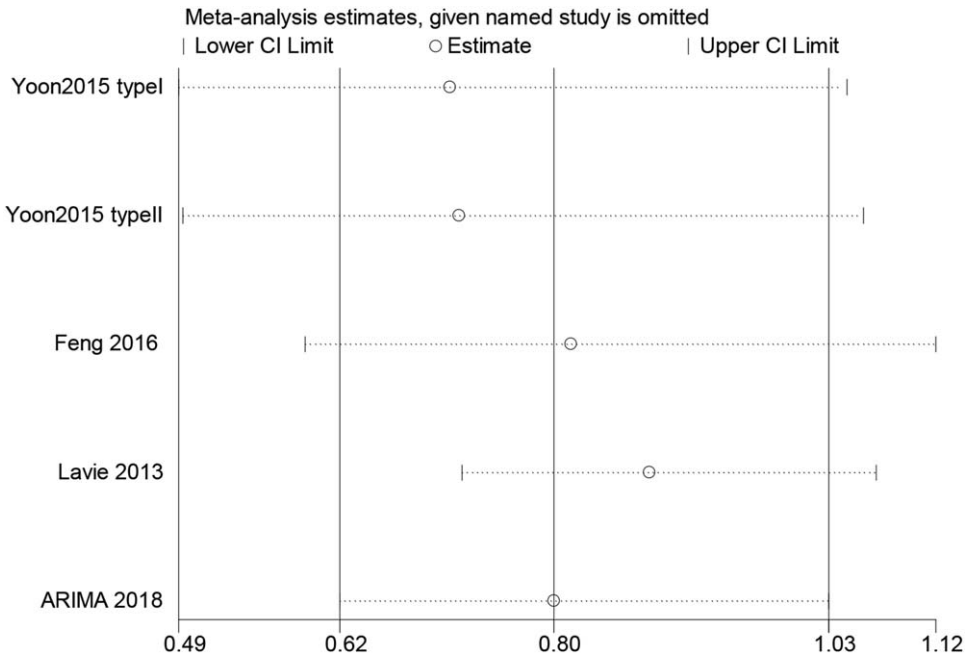

Figure 5. Analysis of sensitivity analysis of the relationship between statin use and overall survival (OS) in patients with endometrial cancer (EC).

Our findings were consistent with those of a recent meta-analysis regarding the positive effect of statins on OS in gynecologic cancer. In our analysis based on histology type, the use of statins was related to an improvement in DSS of type II EC, which was not mentioned in the previous related meta-analysis. This finding is of value for clinically determining treatment programs based on histology type.

Previous studies indicated that using statins may decrease the incidence and mortality of breast, colon, pancreas, gastrointestinal tract, liver, endometrial, and ovarian cancers.[40–44] For EC, obesity is a major risk factor. Obese patients often have hypercholesterolemia, hypertriglyceridemia, diabetes, insulin resistance, and other diseases, which contribute to the occurrence and development of EC and may be associated with an increase in adverse outcomes.[36] Therefore, it is reasonable for patients with EC to use statins, which can reduce triglyceride and cholesterol levels. Several potential mechanisms can explain the positive role of statins in increasing the survival rate of patients with EC.

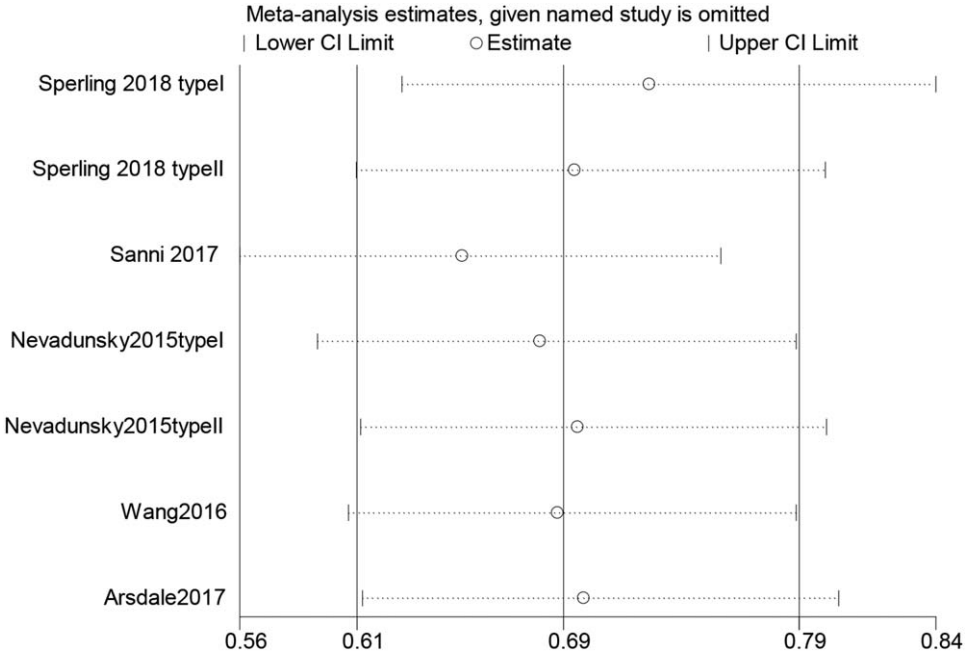

Figure 6. Analysis of sensitivity analysis of the relationship between statin use and DSS in patients with endometrial cancer (EC).

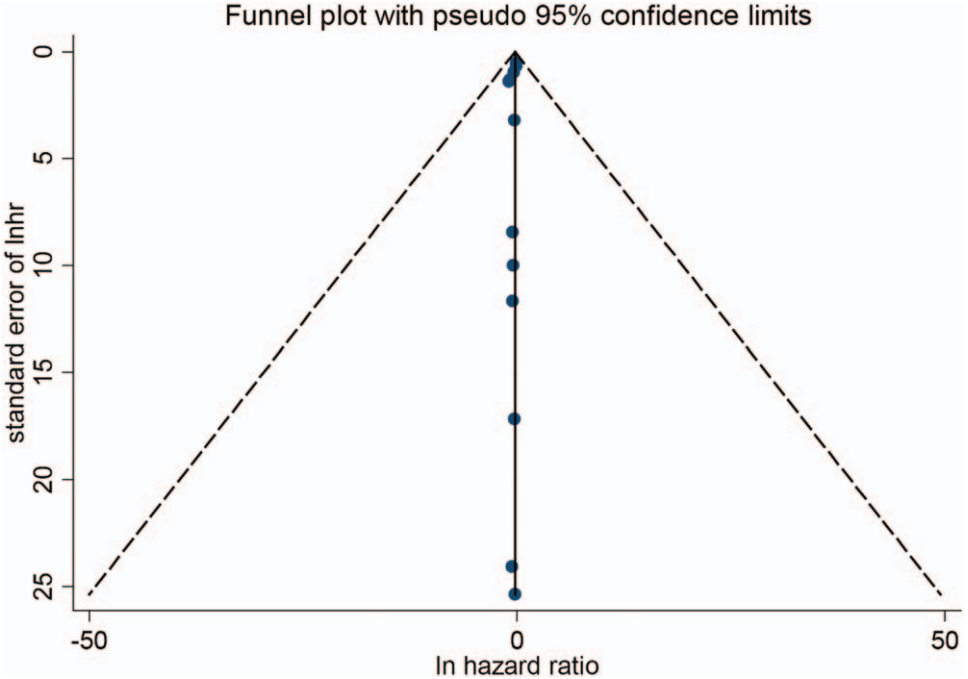

Figure 7. Funnel plot analysis of potential publication bias in the meta-analysis.

Statins can inhibit the mevalonate pathway to mitigate the growth of cancer cells, thereby preventing the prenylation of the essential proteins (Ras and Rho) involved in the migration and proliferation of cancer cells.[45] Statins can stimulate inflammatory responses and anticancer immune surveillance via phosphorylated Akt and downregulation of the mammalian rapamycin target protein (mTOR).[46] Statins can also lower cholesterol, induce apoptosis, and impair metastasis by blocking cellular adhesion and invasion in vitro.[47,48] These mechanisms associated with lipid metabolism and tumor growth may explain the effects of statin on cancer mortality.[49] In conclusion, statins have antiproliferative and antimetastatic effects, which can reduce the cancer mortality rates for statin users.[17]

Although some achievements have been made in this field of research, the results are still currently inconclusive. A retrospective study of the Danish population discovered a significant 15% reduction in all-cancer mortality in patients who took statins.[23] However, Yoon et al found no notable correlation between statin use and EC survival, which implied no significant difference in the mortality risks between statin users and non-statin users.[34] Our results showed that the use of statins can improve the OS (HR 0.80; 95% CI, 0.66–0.95), the DSS (HR 0.69; 95% CI, 0.61–0.79) and type II DSS (HR 0.64; 95% CI, 0.50–0.81) of patients with EC. No significant heterogeneity was found, which helped ensure the accuracy of our results. And the results of sensitivity analysis were also stable. We found sufficient evidence that using statins improved the DSS and type II DSS of EC. The results showing that the use of statins improved the OS of EC were flawed. To better understand the causes of the inconclusive results, we conducted further analyses of the original data. We found that the sample size of the study that evaluated the relationship between the use of statins and the OS of patients with EC was relatively small compared to that of other studies. This may be a major cause of the inconclusive results. There was a significant difference in the prognosis of different histological types of EC. The most common lesion (type I) is usually hormone-sensitive and has a good prognosis in the early stages; however, type II tumors are of high recurrence even in the early stages.[1] We explored the findings regarding type II DSS and found that the use of statins significantly ameliorated type II DSS, which has not been explored before. This finding is essential for improving the prognosis of the disease and is certainly significant for the future use of the drugs in clinical settings.

There were several limitations of this meta-analysis. First, all the included articles were nonrandomized studies, most of which were retrospective studies. Thus, the risk of recall bias was inevitable, and the actual effects of statins might be overestimated because of the lack of random allocation to the interventions. The only 1 prospective study, although not very influential on the overall results, was somewhat weak in persuasiveness. Second, in the included studies, cancer information, such as information on the primary treatment and the definition of OS, DSS, and PFS, was inadequately presented or not clearly described, which might lead to bias. Third, the present study was not registered, and there may be minor deviations. But we still wrote in strict accordance with the steps of system evaluation. Finally, it may be difficult to accurately evaluate the methodological qualities since 1 abstract without full text was included.

Despite these limitations, the study had sufficient strengths to justify the results. We are the 1st to analyze the effect of statins on DSS, especially type II DSS of EC. The OS, DSS, and type II DSS analyses included in our meta-analysis had no significant heterogeneity, which ensures the reliability of our results. All the studies included in the meta-analysis had high quality assessment scores, and no instability was found in the sensitivity analysis, which also enhances the reliability of our results.

5. Conclusion

The results suggested that statin use is significantly associated with beneficial outcomes in EC. In summary, taking statins after the diagnosis of EC can still prolonged the survival.

Author contributions

Conceptualization: Jia Li.
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Formal analysis: Wenge Zhao.
Methodology: Shifeng Tang, Lu Wang.
Software: Lu Wang, Cun Liu.
Supervision: Changgang Sun.
Validation: Yan Yao.
Writing – original draft: Jia Li, Ruijuan Liu, Zhengdi Sun.
Writing – review & editing: Jia Li, Ruijuan Liu, Shifeng Tang.

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