Statin use improves the prognosis of ovarian cancer: An updated and comprehensive meta-analysis

QINGXUE WANG[1,2*], ZHENG ZHI[3*], HUA HAN[4], QINGTAO ZHAO[5], XING WANG[6], SHUMIN CAO[7] and JING ZHAO[2]

[1]Graduate School, Hebei North University, Zhangjiakou, Hebei 075000; [2]Department of Oncology, Hebei General Hospital, Shijiazhuang, Hebei 050051; [3]Department of Basic Medicine, Hebei University of Chinese Medicine, Shijiazhuang, Hebei 050200; Departments of [4]Gynecology and [5]Thoracic Surgery; [6]Clinical Medical Research Center and Geriatric Key Laboratory, Hebei General Hospital, Shijiazhuang, Hebei 050051; [7]Department of Internal Medicine, Hebei Medical University, Shijiazhuang, Hebei 050017, P.R. China

Received September 7, 2022; Accepted November 16, 2022

DOI: 10.3892/ol.2022.13648

Abstract. Statins are lipid-lowering agents that have also been found to have anticancer effects. The relationship between statin use and clinical outcomes in ovarian cancer (OC) remains controversial, as previous assessments of the relationship between statin use and OC prognosis have yielded inconsistent results. Therefore, a comprehensive meta-analysis was performed in the present study to investigate this association. Studies were systematically retrieved by searching the PubMed, Embase and Cochrane Library databases, and consulting reference lists of the related studies. The search timeframe was from database creation to September 1, 2022. Pooled hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were calculated to assess the association. In the present meta-analysis, 16 studies with 37,660 patients with OC were included, of which 11,296 patients had been prescribed statins. The results showed that statin use markedly improved the overall survival time (OS; HR, 0.79; 95% CI, 0.73-0.85; P<0.00001) and OC-specific survival time (HR, 0.84; 95% CI, 0.80-0.89; P<0.00001), especially the OS time in patients with serous OC (HR, 0.81; 95% CI, 0.74-0.89; P<0.0001) and endometrioid OC (HR, 0.80; 95% CI, 0.66-0.98; P=0.03). In addition, survival rate was higher in patients who used statins after OC diagnosis (HR, 0.79; 95% CI, 0.73-0.85; P<0.00001). However, there was no statistically significant association between statin use and the prognosis of mucinous and clear cell OC. The results suggested that statin use markedly improved the OS in patients with OC, including in those with serous and endometrioid OC. Statins were also found to improve the prognosis of patients of both Asian and non-Asian ethnicities. In addition, both lipophilic and hydrophilic statins improved the survival in patients with OC, especially in patients using statins after OC diagnosis. However, the effect may vary depending on the statin type, duration of use and cancer type, and more well-designed studies are needed to further evaluate this.

Correspondence to: Dr Jing Zhao, Department of Oncology, Hebei General Hospital, 348 Heping West Road, Xinhua, Shijiazhuang, Hebei 050051, P.R. China
E-mail: zzzjmail@163.com

Key words: ovarian cancer, statin, prognosis, lipid-lowering agents, overall survival

Introduction

Ovarian cancer (OC) is one of the most common malignant tumors in gynecology, second only to cervical and uterine cancer, with the worst prognosis and the highest mortality rate worldwide (1,2). It is estimated that 39,306 people will die of OC in China in 2022 (3). OC directly and indirectly adds a high economic burden on society (4). The main reason for the high mortality rate is the insidious onset of OC and the lack of effective screening tools; consequently, >70% of patients are already at an advanced stage at the time of diagnosis (5). OC treatment is based on aggressive cytoreductive surgery combined with platinum chemotherapy. However, the prognosis of OC remains unsatisfactory, despite the emergence of new chemotherapeutic and targeted agents in recent years (6). Therefore, there is an urgent need to identify simple methods to reduce the risk of OC development, and improve the prognosis and quality of life of patients with OC. In previous years, it has been found that obesity and hyperlipidemia can increase the risk of OC, and lead to a poor prognosis (7). Statins, which are widely used in clinical practice, are the most commonly used lipid-lowering drugs. The effects of statins have been found to be multi-functional, including not only the lowering of blood lipids, but also the suppression of tumor proliferation and the promotion of cell apoptosis (8-10). Some studies have reported that statins are associated with a reduced risk of developing OC (11,12). However, relatively few studies have been conducted on the association between the use of statins and the prognosis of OC.

Obesity and hyperlipidemia are risk factors, as well as prognostic factors, for OC, which directly affect the survival

rate of patients (13). Some previous studies showed that statin treatment improved the prognosis of OC; however, other studies did not reach similar conclusions (14-16). Therefore, the current evidence on the prognostic effects of lipid-lowering drugs on OC is inconsistent and is insufficient to form a reliable conclusion to provide a scientific basis for clinical treatment. Moreover, to the best of our knowledge, there is no meta-analysis considering the heterogeneous effects of the type of statin, mode of use, pathological type and clinical stage of OC. Therefore, a comprehensive updated meta-analysis was performed to guide the clinical application of statins in OC.

Materials and methods

Search methods and study selection criteria. A comprehensive literature search of articles was performed using the following databases: PubMed (https://pubmed.ncbi.nlm.nih.gov), Embase (http://www.embase.com) and Cochrane Library (https://www.cochranelibrary.com). Case-control trials and cohort studies on statin therapy for OC that had been conducted were included. The search timeframe was from database creation to September 1, 2022. The search was performed using the following subject terms in combination with free terms: i) 'Statins' OR '3-hydroxy-3-methylglutaryl CoA reductase inhibitor' OR 'anticholesteremic' OR 'simvastatin' OR 'atorvastatin' OR 'fluvastatin' OR 'lovastatin' OR 'rosuvastatin' OR 'pravastatin' OR 'pitavastatin'; ii) 'ovarian cancer' OR 'ovarian neoplasms' OR 'ovarian carcinoma'; and iii) 'survival' OR 'prognosis' OR 'mortality' OR 'death' OR 'recurrence' OR 'outcome'. All search terms were restricted to studies involving human subjects in the English language.

Inclusion and exclusion criteria. Studies included in the present meta-analysis met the following inclusion criteria: i) The diagnosis of OC was pathologically confirmed; ii) association between statin use and overall survival (OS), progression-free survival (PFS) and/or OC-specific survival (OVS) were reported; iii) studies were designed as cohort studies or case-control studies; and iv) adjusted hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were available. The following studies were excluded: i) Abstracts, editorials, posters, newsletters, preclinical studies, case reports, reviews, meta-analyses or non-clinical studies; ii) studies not in the English language; iii) studies with insufficient data to estimate the HRs and 95% CIs; iv) studies with duplicate data or repeated analyses; and v) *in vitro* studies.

Data extraction. Two researchers independently screened the literature, extracted information and assessed the study quality based on the predetermined inclusion criteria. Articles that could not be classified by screening the title and abstract were assessed by searching the entire text. Any inconsistencies were resolved by consultation with the corresponding author. The extracted information mainly included: i) Basic information of the studies, including the first author, year of publication, country, study design and study type; ii) baseline characteristics of the study population, including the characteristics of the patients, sample size, mean age, type of statin use, follow-up duration and definition of statin use; and iii) information on the interventions, outcome indicators and risk of bias assessment. The quality of each study was evaluated using the Newcastle-Ottawa Scale (17), shown in Table I. This scale ranges from 1 to 9 stars and judges the quality of each study based on three aspects: i) Selection of the study groups; ii) comparability of the groups; and iii) ascertainment of the outcome of interest. NOS scores of ≥6 were assigned as high-quality studies, while scores of <6 were considered low-quality studies.

Statistical analysis. HRs and 95% CIs were directly obtained from each study or estimated according to the methods described by Parmar *et al* (18). An HR >1 indicated a worse prognosis for patients with OC. Cochran's Q test and Higgins I-squared statistics were used to assess the heterogeneity among the included studies, and a value of <0.10 was used to indicate heterogeneity. The choice between fixed-effects and random-effects meta-analyses should not be based on statistical tests of heterogeneity, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions (https://training.cochrane.org). Heterogeneity in intervention effects between multiple studies from different groups and geographical locations will always occur. Therefore, all forest plots in the present study used a random-effects model to account for this. Publication bias was assessed using Begg's funnel plot (19) and Egger's regression test. All P-values were two-sided. $P<0.05$ was considered to indicate a statistically significant difference. Statistical analysis was performed using RevMan 5.3 software (Nordic Centre) and STATA 15.0 (StataCorp LLC).

Results

Description of included studies. The initial search strategy retrieved 402 studies, and after careful review, 16 were ultimately included (12,20-34). These 16 studies were published from 2008-2022 and contained a total of 37,660 patients with OC, of whom 11,296 were statin users. The study selection process is summarized in the flow chart in Fig. 1. Of the included studies, 4 were conducted on Asian participants (12,27,31,32) and 12 on non-Asian participants (20-26,28-30,33,34). In total, 5 studies were from the United States of America (20,22,23,28,34), 2 were conducted each in Australia (25,29), Denmark (24,33) and Israel (12,27), and 1 study was conducted each in Korea (31), China (32), Canada (30), Finland (21) and Belgium (26). All studies directly reported HRs and 95% CIs, and 4 studies enrolled <200 patients with OC (12,20,27,32). Among the included studies, 13 were cohort studies (21-31,33,34) with a total sample size of 37,324, while 3 were case-control studies (12,20,32) with a total sample size of 336. Overall, 3 prospective studies (25,33,34) and 13 retrospective studies (12,20-24,26-32) were included. All the studies reported a correlation between statin use and OC prognosis. The characteristics of the included studies are shown in Table II.

Association between statin use and prognosis of OC. All included studies reported HRs and their respective 95% CIs, and OS time, while some also reported OVS and/or PFS. The studies were therefore divided into three categories according to the study endpoint (Fig. 2). It was determined that the use of

Table I. Details of study quality evaluation via the NOS.

	NOS score										
First author, year	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Control for age	Control for other confounding factors	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts	Total	(Refs.)
Elmore *et al*, 2008	1	1	1	1	0	1	0	1	1	7	(20)
Urpilainen *et al*, 2018	1	1	1	1	0	1	0	1	1	7	(21)
Habis *et al*, 2014	0	1	1	1	1	1	0	1	1	7	(22)
Vogel *et al*, 2017	1	1	1	1	1	1	1	1	1	9	(23)
Verdoodt *et al*, 2017	1	1	1	1	1	1	1	1	1	9	(24)
Majidi *et al*, 2021	1	1	1	0	0	1	1	1	1	7	(25)
Couttenier *et al*, 2017	1	1	1	1	0	1	1	1	1	8	(26)
Bar *et al*, 2016	1	1	1	1	1	1	1	1	1	9	(27)
Harding *et al*, 2019	1	1	1	1	0	1	1	1	1	8	(28)
Feng *et al*, 2021	1	1	1	1	1	1	1	1	1	9	(29)
Hanley *et al*, 2021	1	1	1	1	1	1	1	1	1	9	(30)
Kim *et al*, 2022	1	1	1	1	1	0	1	1		8	(31)
Chen *et al*, 2016	1	1	1	1	1	0	1	1	1	8	(32)
Lavie *et al*, 2013	1	1	0	1	1	1	0	1	1	8	(12)
Nielsen *et al*, 2012	1	1	1	1	1	1	1	1	1	9	(33)
Wang *et al*, 2016	1	1	1	1	1	0	0	1	1	7	(34)

NOS, Newcastle-Ottawa scale.

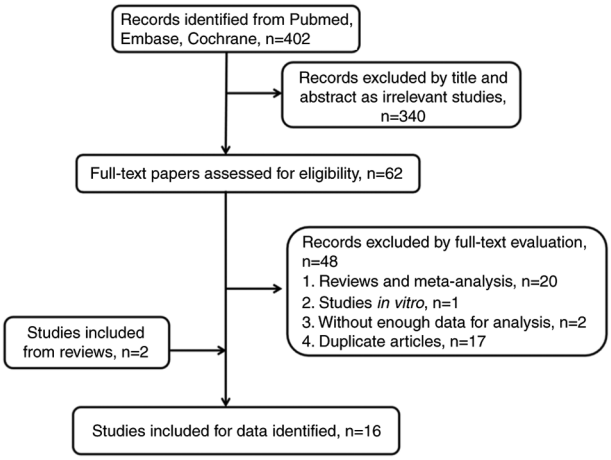

Figure 1. Flow chart of the study search and screening for the present meta-analysis.

statins significantly prolonged the OS time (HR, 0.79; 95% CI, 0.73-0.85; P<0.00001) and markedly increased the OVS time (HR, 0.84; 95% CI, 0.80-0.89; P<0.00001) of patients with OC; no statistical difference was observed in the PFS time (HR, 0.96; 95% CI, 0.74-1.25; P=0.77).

Subgroup analysis by type of statin. Statins can be divided into two categories based on their solubility: Hydrophilic statins (pravastatin and rosuvastatin) and lipophilic statins (simvastatin, lovastatin, fluvastatin and atorvastatin). The HRs and 95% CIs for OC mortality with lipophilic and hydrophilic statins, were each reported in 6 studies. It was observed that the type of statin used had a statistically significant effect on the prognosis of OC (lipophilic statins: HR, 0.82; 95% CI, 0.73-0.91; P=0.0003; hydrophobic statins: HR, 0.81; 95% CI, 0.73-0.90; P<0.0001; Fig. 3). A statistically significant effect on the prognosis of OC regardless of the type of statins used was therefore observed.

Subgroup analysis by usage of statins. Of the 16 studies, 3 reported the significance of new and continuous statin use on OC prognosis. It was observed that new statin users were associated with reduced OC mortality (HR, 0.70; 95% CI, 0.57-0.86; P=0.0006), whereas no significant association with OC prognosis was observed in continuous statin users (HR, 0.83; 95% CI, 0.65-1.05; P=0.12) (Fig. 4). A total of 13 studies reported the association between post-diagnostic statin use and OC prognosis, showing that post-diagnostic statin use improved OC prognosis (HR, 0.79; 95% CI, 0.73-0.85; P<0.00001), while no statistically significant association was observed with pre-diagnostic statin use (HR, 0.87; 95% CI, 0.75-1.01; P=0.06; Fig. 5).

Subgroup analysis by type of OC. Clinically, OC is a heterogeneous disease with four distinct histological subtypes: Serous, endometrioid, clear cell and mucinous OC, each with its own unique clinical, genetic and molecular features. Subgroup analysis (Fig. 6) showed that statin use significantly improved the survival in patients with serous (HR, 0.81; 95% CI, 0.74-0.89; P<0.0001) and endometrioid (HR, 0.80; 95% CI, 0.66-0.98; P=0.03) OC, whereas no significant association was observed in patients with clear cell (HR, 0.94; 95% CI, 0.71-1.25; P=0.68) and mucinous (HR, 1.02; 95% CI, 0.67-1.54; P=0.93) OC. This may be related to the low prevalence of these two pathological types, which resulted in a small number of enrolled cases. It is evident that the protective effect of statins in improving OC survival may be limited to specific OC subtypes.

Subgroup analysis by grades of serous OC. The relationship between statin use and OS with regard to the histological subtypes of serous OC was further evaluated in order to explore whether statin use was associated with an improved prognosis in different grades of serous OC (Fig. 7). The results showed that statins prolonged the OS in patients with high-grade serous OC (HR, 0.82; 95% CI, 0.70-0.96; P=0.01), but statin use did not show a statistical difference in patients with low-grade serous OC subtypes (HR, 0.52; 95% CI, 0.23-1.18; P=0.12).

Subgroup analysis by stages of OC. In a subgroup analysis of staging at diagnosis, statins reduced the mortality in patients with stage III-IV OC (HR, 0.74; 95% CI, 0.64-0.85; P<0.0001), whereas no statistical association was observed between statin use and prognosis in patients with stage I-II OC (HR, 0.80; 95% CI, 0.53-1.21; P=0.29) (Fig. 8).

Subgroup analysis by ethnicity. Patients in the 16 studies were divided into Asian and non-Asian groups, according to ethnicity. Statins were found to improve the prognosis of OC in patients of Asian and other ethnicities (HR, 0.79; 95% CI, 0.73-0.85; P<0.00001; Fig. 9).

Subgroup analysis by study design. Of the 16 studies included, 3 were prospective studies and the remainder were retrospective studies. The results of the subgroup analysis (HR, 0.79; 95% CI, 0.73-0.85; P<0.00001; Fig. 10) showed that both prospective and retrospective studies found that statins improved OC prognosis.

Heterogeneity and sensitivity analyses. Except for the results of the subgroup analyses on patients with OC taking continuous statins (I^2, 65%; P=0.06), those taking lipophilic statins (I^2, 61%; P=0.03), those taking statins before OC diagnosis (I^2, 84%; P<0.00001), patients of non-Asian ethnicity taking statins (I^2, 53%; P=0.01), prospective studies (I^2, 69%; P=0.04) and mucinous patients taking statins (I^2, 60%; P=0.04), heterogeneity was not significant in most of the studies analyzed. These values all indicate heterogeneity in subgroup analysis results. After careful reading of the literature and a sensitivity analysis, it was found that Feng *et al* (29) may be the source of heterogeneity. The pooled HRs calculated by random effects models for these heavily heterogeneous subgroup analyses were not significantly associated and the pooled results were stable in sensitivity analyses. Sensitivity analyses showed no change in the direction of effect when omitting one study at a time, and the pooled results were similar to the overall results (HR, 0.83; 95% CI, 0.79-0.86; Fig. 11). Notably, the results of most studies in the subgroup analysis were statistically significant and consistent with the primary results.

Publication bias. Using funnel plots (Fig. 12), Begg's test (Fig. 13) and Egger's regression test (Fig. 14) to assess for

Table II. Characteristics of the included studies.

First author, year	Country	Patient ethnicity	Type of study	Study design	Study period, year range	Patients, n	Patients prescribed statins, n	Statin exposure	Statins prescribed pre- or post-diagnosis	HR (95% CI)	Follow-up time	(Refs.)
Elmore *et al*, 2008	USA	Non-Asian	Case-control	Retrospective	1996-2001	126	17	Lipophilic and hydrophilic	Post	0.45 (0.23-0.88)	4.5 years (median)	(20)
Urpilainen *et al*, 2018	Finland	Non-Asian	Cohort	Retrospective	1998-2011	421	186	Lipophilic	Pre	0.72 (0.56-0.93)	2.2 years[a]	(21)
Habis *et al*, 2014	USA	Non-Asian	Cohort	Retrospective	1992-2013	442	68	Lipophilic and hydrophilic	Post	0.80 (0.50-1.29)	3.5 years[a]	(22)
Vogel *et al*, 2017	USA	Non-Asian	Cohort	Retrospective	2007-2009	1,431	609	Lipophilic and hydrophilic	Post	0.62 (0.50-0.77)	2.6 years (median)	(23)
Verdoodt *et al*, 2017	Denmark	Non-Asian	Cohort	Retrospective	2000-2013	4,419	476	Lipophilic and hydrophilic	Post	0.90 (0.78-1.04)	2.4 years (median)	(24)
Majidi *et al*, 2021	Australia	Non-Asian	Cohort	Prospective	2012-2015	955	199	Lipophilic and hydrophilic	Both	0.73 (0.52-1.03)	5.0-8.0 years[a]	(25)
Couttenier *et al*, 2017	Belgium	Non-Asian	Cohort	Retrospective	2004-2012	5,416	1,255	Lipophilic and hydrophilic	Both	0.81 (0.72-0.90)	0.5 to 3.0 years[a]	(26)
Bar *et al*, 2016	Israel	Asian	Cohort	Retrospective	2000-2012	143	43	NA	Post	0.69 (0.41-1.17)	4.1 years (median)	(27)
Harding *et al*, 2019	USA	Non-Asian	Cohort	Retrospective	2007-2012	2,195	489	Lipophilic and hydrophilic	Post	0.74 (0.61-0.91)	2.2 years[a]	(28)
Feng *et al*, 2021	Australia	Non-Asian	Cohort	Retrospective	2003-2013	8,629	1,897	Lipophilic and hydrophilic	Both	0.87 (0.82-0.94)	19.0 years[a]	(29)

Table II. Continued.

First author, year	Country	Patient ethnicity	Type of study	Study design	Study period, year range	Patients, n	Patients prescribed statins, n	Statin exposure	Statins prescribed pre- or post-diagnosis	HR (95% CI)	Follow-up time	(Refs.)
Hanley *et al*, 2021	Canada	Non-Asian	Cohort	Retrospective	1997-2015	4,207	535	Lipophilic and hydrophilic	Both	0.80 (0.69-0.93)	3.0 years[a]	(30)
Kim *et al*, 2022	Korea	Asian	Cohort	Retrospective	2005-2013	677	160	Lipophilic and hydrophilic	Post	0.70 (0.40-1.21)	7.6 years[a]	(31)
Chen *et al*, 2016	China	Asian	Case-control	Retrospective	2009-2013	60	35	NA	Post	0.57 (0.21-1.51)	2.5 years (median)	(32)
Lavie *et al*, 2013	Israel	Asian	Case-control	Retrospective	2003-2010	150	67	NA	Post	0.24 (0.06-0.78)	9.0 years (median)	(12)
Nielsen *et al*, 2012	Denmark	Non-Asian	Cohort	Prospective	1995-2007	8,159	5,213	Lipophilic and hydrophilic	Pre	0.93 (0.81-1.08)	2.6 years median	(33)
Wang *et al*, 2016	USA	Non-Asian	Cohort	Prospective	1993-1998	230	47	Lipophilic and hydrophilic	Pre	0.58 (0.40-0.85)	14.6 years median	(34)

[a]Median was not stated. CI, confidence interval; HR, hazard ratio; NA, (data) not available; NOS, Newcastle-Ottawa scale.

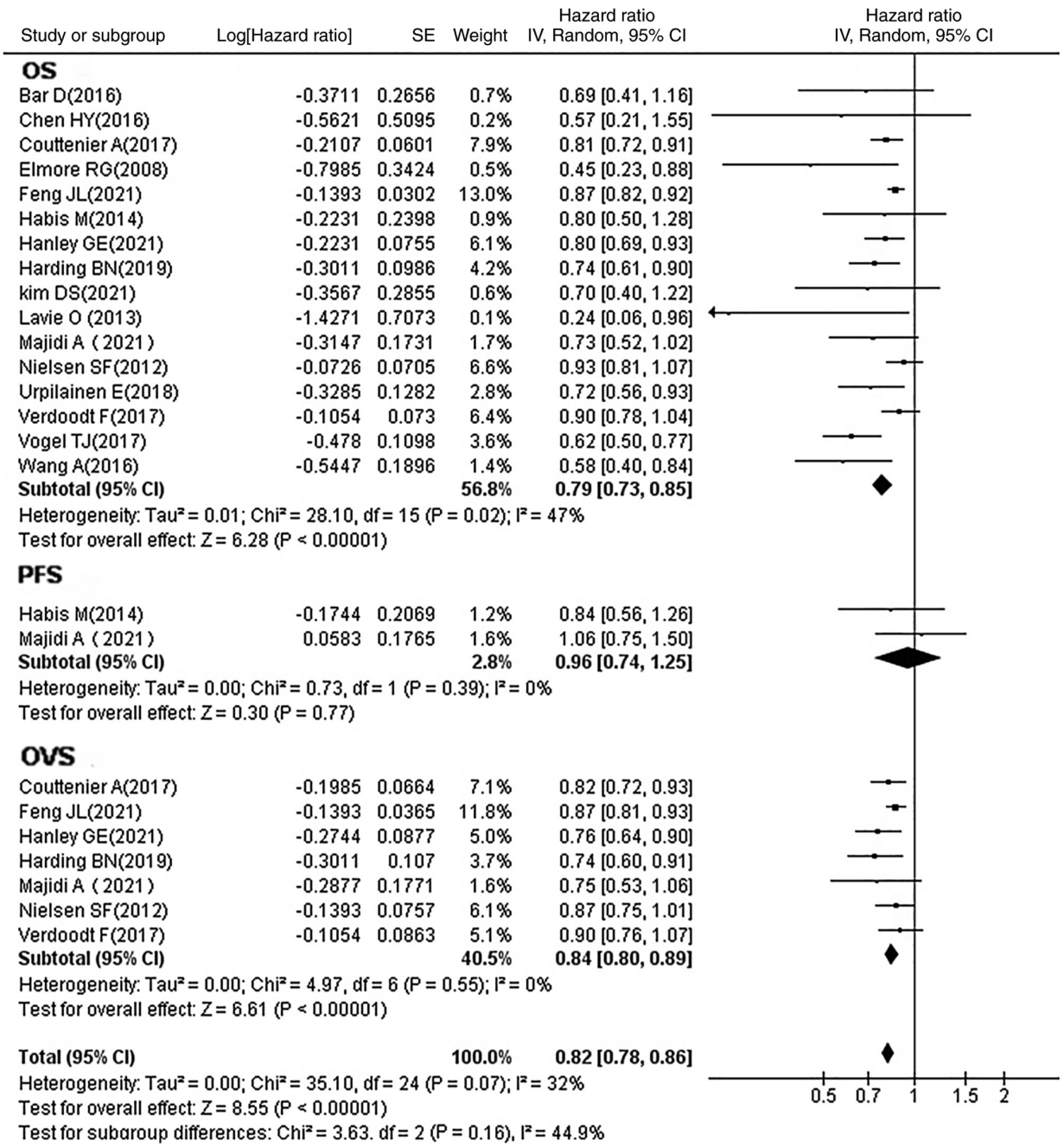

Figure 2. Forest plot for the association between statin use and prognosis of ovarian cancer, using a random-effects model. The squares with the corresponding horizontal line represent the HR and 95% CI of each study. The area of the square reflects the weight of the study. The diamond represents the pooled HR and 95% CI. CI, confidence interval; HR, hazard ratio; IV, inverse variance model; OS, overall survival; OVS, ovarian cancer-specific survival; PFS, progression-free survival; SE, standard error.

publication bias, the Begg's (P=0.027) and Egger tests (P=0.001) did detect publication bias, and examination of funnel plots showed visual asymmetry. In similar studies, statistically significant findings were more likely to be published than non-statistically significant findings, which may lead to publication bias.

Discussion

Since OC starts insidiously and lacks effective detection methods in the early stages of the disease, most patients are already in an advanced stage at the time of diagnosis. Although there have been rapid developments in chemotherapy, targeted therapy and immunotherapy for OC, the 5-year OS rate of patients with OC is <50% (35), and there is recurrent relapse, which is not easily curable. There is an urgent need to improve the prognosis of patients with OC or to achieve an improved synergy with therapy. Therefore, the present study focused on improving prognosis and prolonging the survival time of patients with OC.

In the present study, the relationship between statin use and the prognosis of patients with OC was investigated

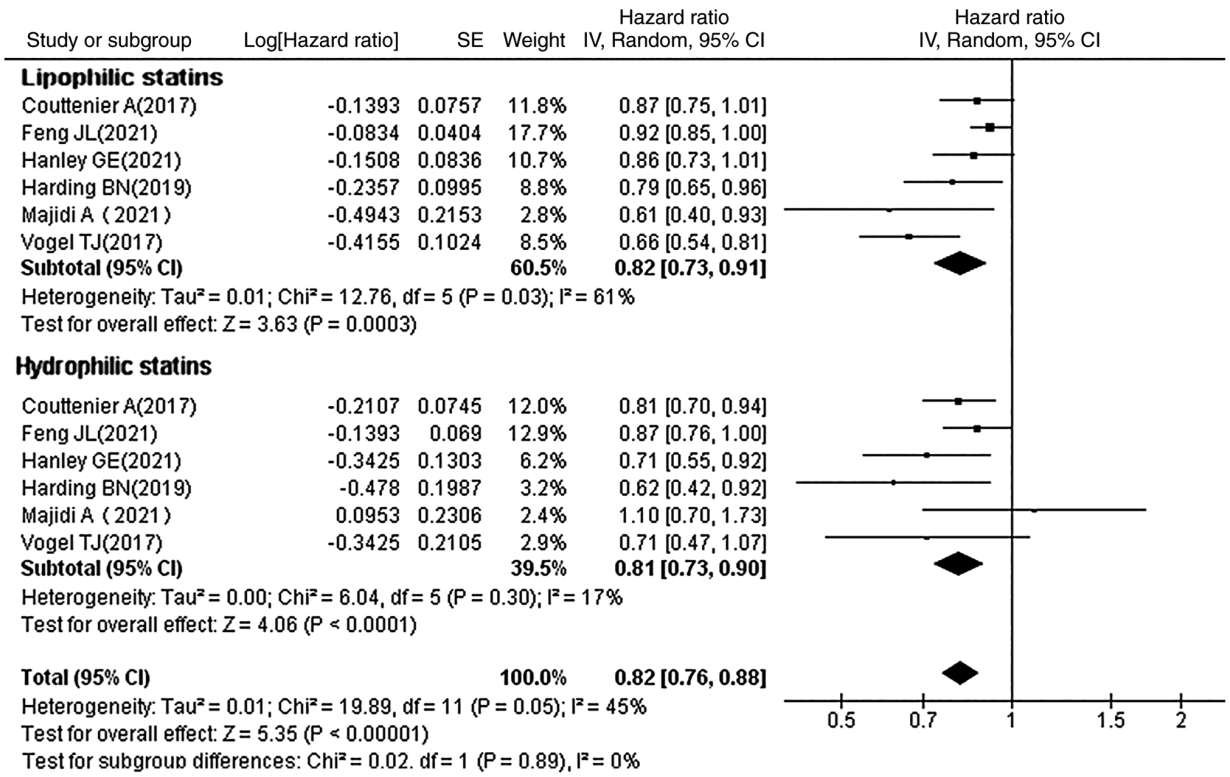

Figure 3. Subgroup analyses for the association between the different types of statins used and the prognosis of ovarian cancer, using a random-effects model. The squares with the corresponding horizontal line represent the HR and 95% CI of each study. The area of the square reflects the weight of the study. The diamond represents the pooled HR and 95% CI. CI, confidence interval; HR, hazard ratio; IV, inverse variance model; SE, standard error.

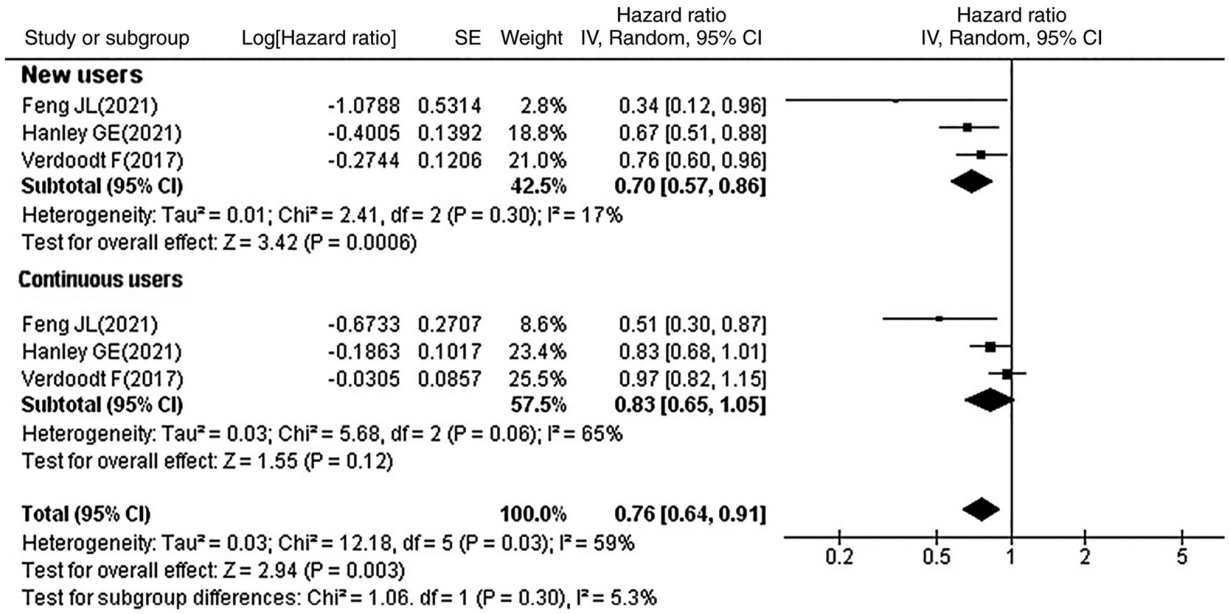

Figure 4. Subgroup analyses for the association between the different usage of statins (new users vs. continuous users) and the prognosis of OC, using a random-effects model. The squares with the corresponding horizontal line represent the HR and 95% CI of each study. The area of the square reflects the weight of the study. The diamond represents the pooled HR and 95% CI. New users were defined as patients who started taking statins after OC diagnosis; continuous users were defined as patients with OC who used statins both before and after diagnosis. CI, confidence interval; HR, hazard ratio; IV, inverse variance model; OC, ovarian cancer; SE, standard error.

by analyzing the results of 11,296 patients with OC taking statins, with data from 16 individual studies. The use of statins significantly prolonged the OS time of patients with OC by improving lipid metabolism, suggesting that statins and other lipid-lowering drugs may improve the prognosis of patients with OC by improving lipid metabolism disorders, such as hyperlipidemia. For example, Habis *et al* (22) reported that lowering plasma lipid levels improved the prognosis of

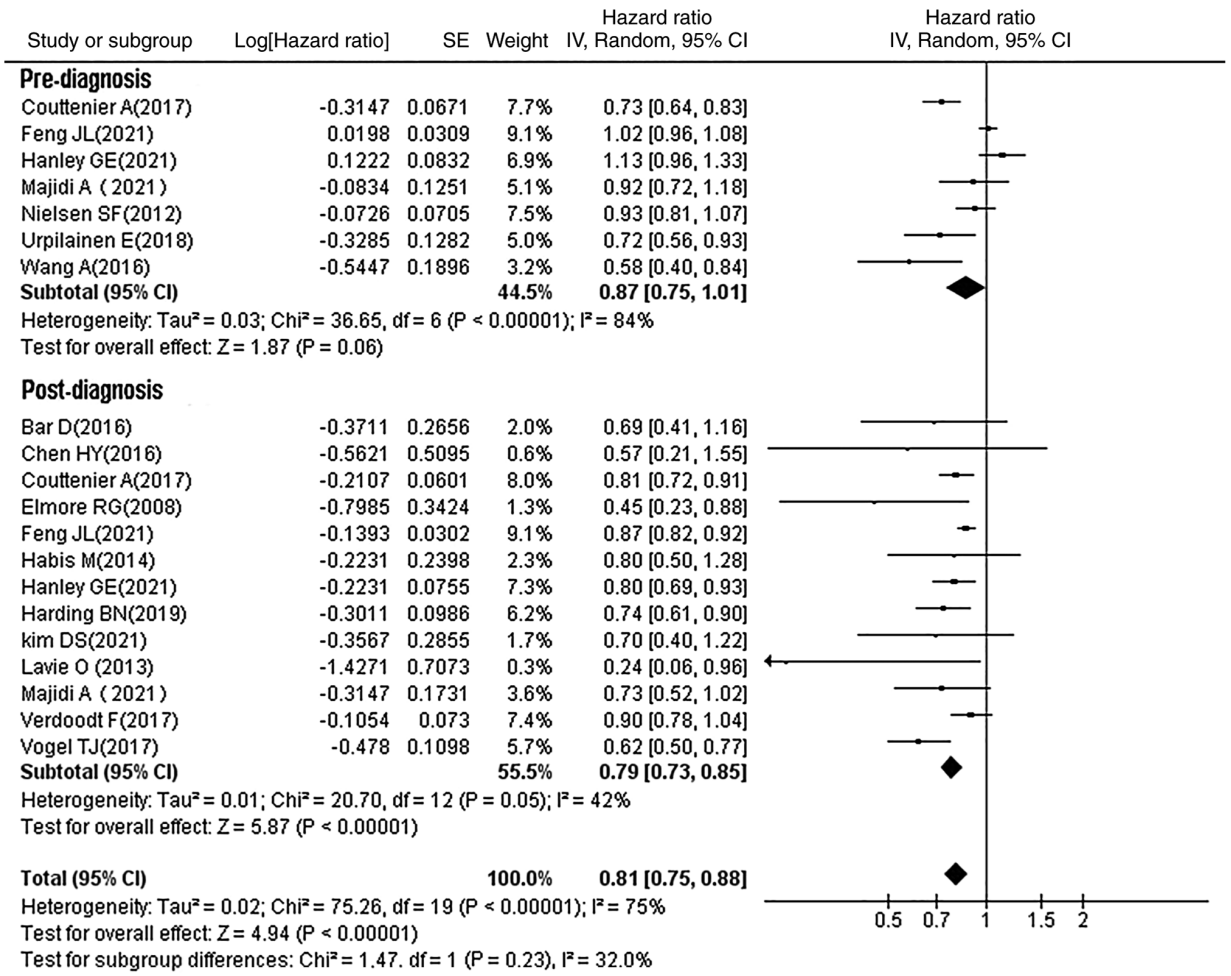

Figure 5. Subgroup analyses for the association between the different usage of statins (pre-diagnosis vs. post-diagnosis) and prognosis of OC, using a random-effects model. The squares with the corresponding horizontal line represent the HR and 95% CI of each study. The area of the square reflects the weight of the study. The diamond represents the pooled HR and 95% CI. Pre/post-diagnosis was defined as before/after OC diagnosis, respectively. CI, confidence interval; HR, hazard ratio; IV, inverse variance model; OC, ovarian cancer; SE, standard error.

patients with OC. Similarly, other studies showed that the clinical application of statins reduced the risk of recurrence and metastasis of breast cancer by improving lipid metabolism disorders (36,37). Four reasons for this improvement were considered, one of which is that lipids are the basic building blocks of the membrane structure, and rapidly dividing cancer cells need more lipids to synthesize this cell membrane (38). In our preliminary study, it was found that inhibiting the exogenous lipid uptake by inhibiting CD36 can significantly inhibit the proliferation and migration of breast cancer cells (39). Statins can reduce the availability of exogenous lipids to cancer cells and thus reduce the uptake of exogenous lipids by cancer cells, thus inhibiting the division and proliferation of tumor cells and playing an antitumor role (35). Secondly, lipids can be metabolized through β-oxidation in a more efficient and effective way to provide more energy to the rapidly proliferating tumor cells. Camarda *et al* (40) showed that inhibition of fatty acid oxidation produced significant antitumor effects. Thirdly, lipids act as signaling molecules and mediate several pro-cancer signaling pathways. Liu *et al* (41) reported that statins induce the apoptosis of OC cells by activating JNK and enhancing Bim expression. Another study by Niemi *et al* (42) suggested that OC is associated with lipid metabolism disorders, and statins induce apoptosis by being involved in signaling pathways, such as Ras/AMP-activated kinase, Janus kinase/stress-activated protein kinase, PI3K/AKT and NF-κB, which inhibit the mevalonate pathway to lower lipid levels and inhibit tumor growth (43-46). Finally, estrogen produced by adipose tissue-derived aromatase is the main source of estrogen in postmenopausal women, and elevated estrogen is associated with the etiology of OC (47). Therefore, obesity is closely related to the occurrence and prognosis of hormone-sensitive OC. Furthermore, obesity is linked to the predisposition to lipid metabolism disorders, such as hyperlipidemia, which indicates that lipid metabolism disorders are risk factors for OC. Therefore, the prognosis of patients with OC improves after successful treatment of lipid metabolism disorders, which was also confirmed in the present study. All the aforementioned mechanisms suggest that statins can affect the prognosis of OC by improving lipid metabolism disorders.

Although the results of the present meta-analysis revealed that statins significantly improved the OS time in patients with OC, the current findings did not yield an association between statin use and the PFS time of patients with OC, and this is likely due to the small sample size studied. Only 2

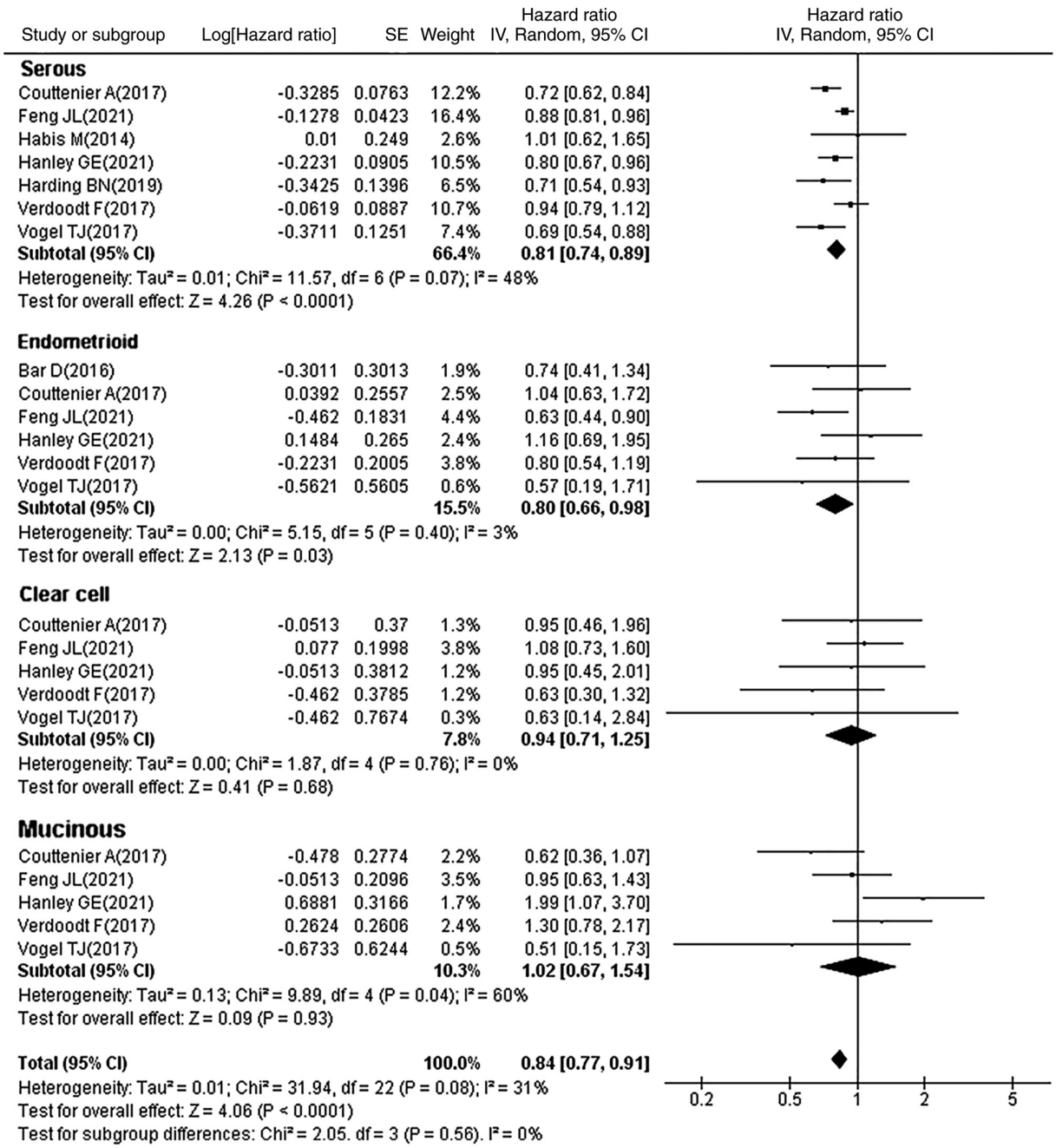

Figure 6. Subgroup analyses for the association between statins and prognosis for different types of ovarian cancer, using a random-effects model. The squares with the corresponding horizontal line represent the HR and 95% CI of each study. The area of the square reflects the weight of the study. The diamond represents the pooled HR and 95% CI. CI, confidence interval; HR, hazard ratio; IV, inverse variance model; SE, standard error.

studies (22,25) analyzed the PFS time. Therefore, more studies are required with PFS as an endpoint.

A subgroup analysis to analyze the association between statin use and the prognosis of different pathological types of OC was performed, which found a significant benefit in patients with serous and endometrioid OC with statin use. Considering that both these pathological types of OC are associated with hormone sensitivity, the result corroborates the fourth mechanism aforementioned. However, no statistical association was observed for the prognosis of patients with mucinous or clear cell OC. This may be related to the low prevalence of these two pathological types, which resulted in a small number of enrolled cases.

There is no clear recommendation on what type of statin to use and how to use them clinically. Therefore, a subgroup analysis on the type and usage of statins was performed in the present study. It was found that the use of statins after OC diagnosis significantly prolonged the survival of patients with OC, while no survival benefit was seen in patients who had been taking such drugs consistently since before diagnosis. It is possible that as medications to improve hyperlipidemia were being consistently used before the diagnosis of OC, the lipid metabolism disorder in such patients was already corrected to some extent at the time of inclusion in the study, which may have led to the absence of an association between lipid-lowering medications and the prognosis

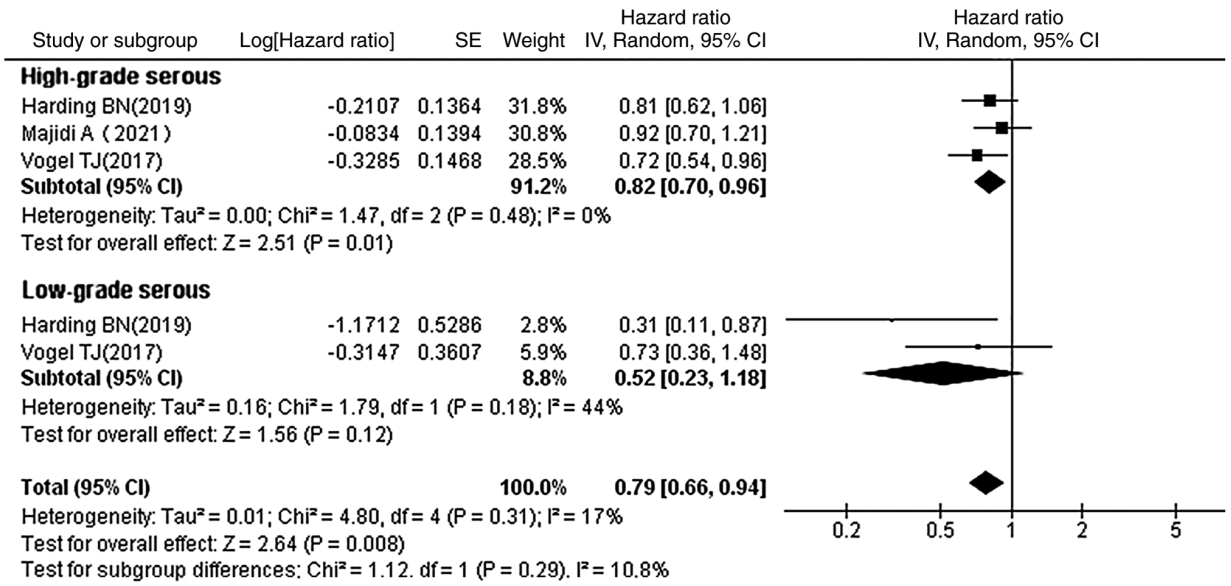

Figure 7. Subgroup analyses for the association between statins and prognosis for different grades of ovarian cancer, using a random-effects model. The squares with the corresponding horizontal line represent the HR and 95% CI of each study. The area of the square reflects the weight of the study. The diamond represents the pooled HR and 95% CI. CI, confidence interval; HR, hazard ratio; IV, inverse variance model; SE, standard error.

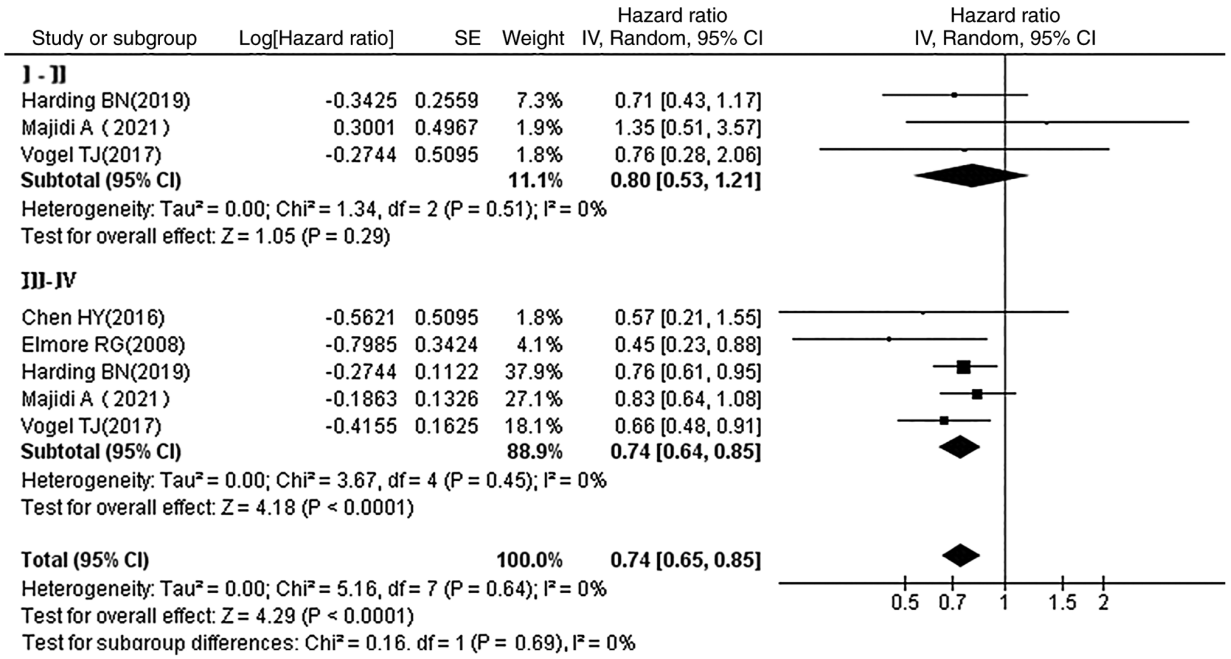

Figure 8. Subgroup analyses for the association between statins and prognosis for different stages of ovarian cancer, using a random-effects model. The squares with the corresponding horizontal line represent the HR and 95% CI of each study. The area of the square reflects the weight of the study. The diamond represents the pooled HR and 95% CI. CI, confidence interval; HR, hazard ratio; IV, inverse variance model; SE, standard error.

of OC. This also suggests that OC is the result of a combination of multiple factors. Others have argued that cancer that develops in the presence of a statin is then 'resistant' to statin use after the diagnosis of OC (29). Based on the results in the present study, it cannot be argued that there is no survival benefit for patients with OC who had been using statins consistently before the OC diagnosis. Regarding the type of statin used, the subgroup analysis revealed that both lipophilic and hydrophilic statins improved the prognosis of patients with OC.

To date, 3 studies have been published on the association between statin use and OC prognosis (14-16), but none of them have considered the heterogeneous effects of the type of statin, mode of use, and the pathological type and clinical stage of OC. The present study incorporates the most recent studies with detailed subgroup analyses to provide more specific scientific evidence for optimal clinical decision-making.

Several limitations of the present meta-analysis should be considered. Firstly, a number of included studies evaluated

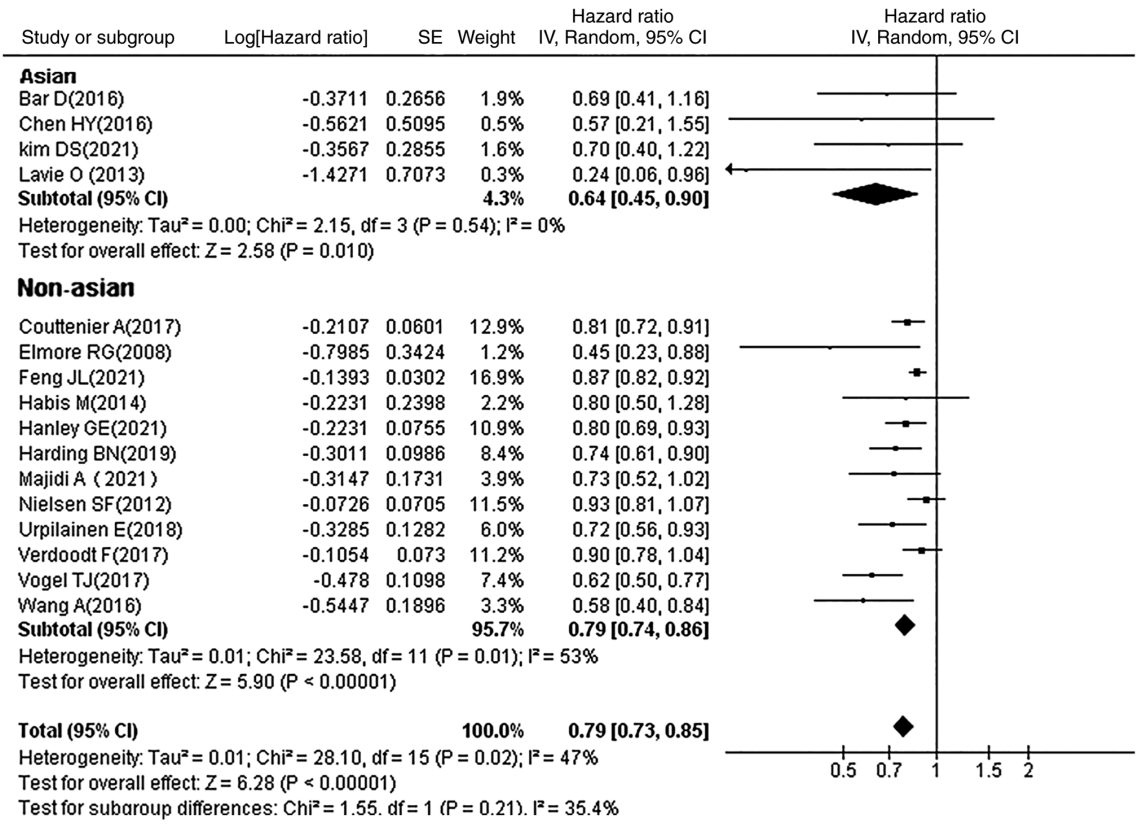

Figure 9. Subgroup analyses for the association between statins and ovarian cancer prognosis in different ethnicities, using a random-effects model. The squares with the corresponding horizontal line represent the HR and 95% CI of each study. The area of the square reflects the weight of the study. The diamond represents the pooled HR and 95% CI. CI, confidence interval; HR, hazard ratio; IV, inverse variance model; SE, standard error.

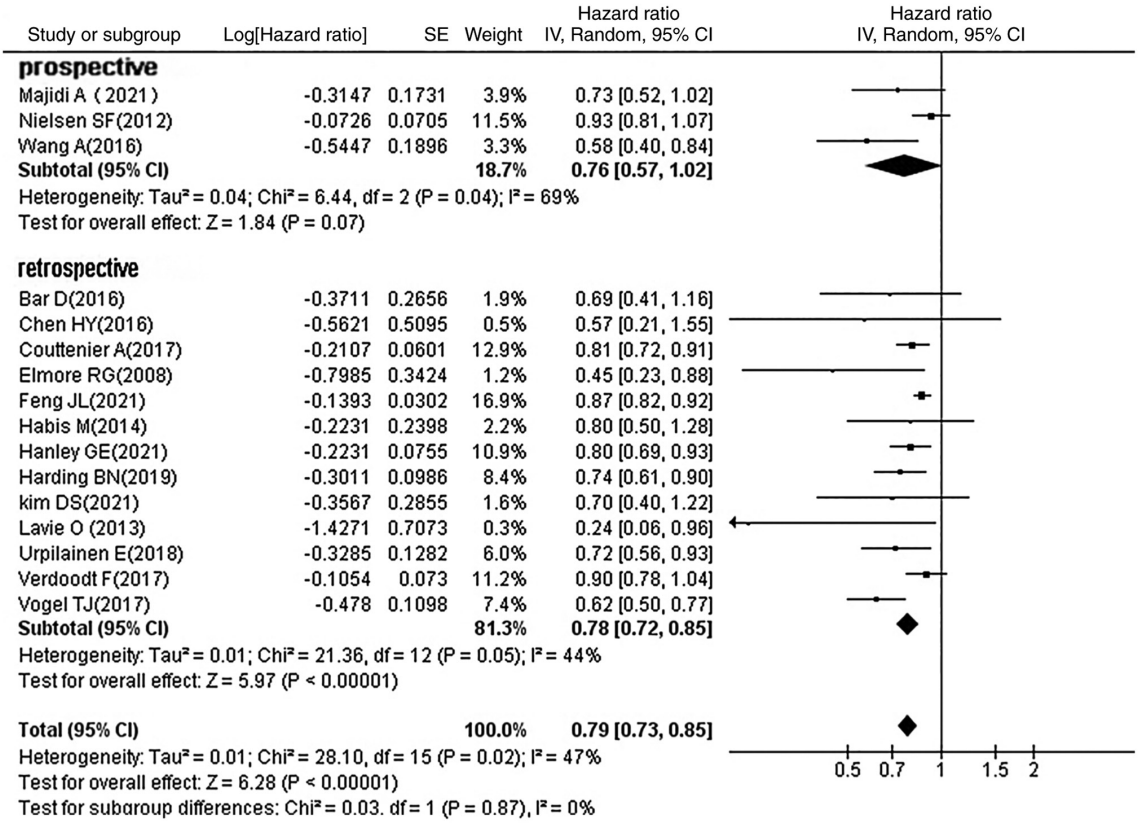

Figure 10. Subgroup analyses for the association between statins and prognosis in different study designs, using a random-effects model. The squares with the corresponding horizontal line represent the HR and 95% CI of each study. The area of the square reflects the weight of the study. The diamond represents the pooled HR and 95% CI. CI, confidence interval; HR, hazard ratio; IV, inverse variance model; SE, standard error.

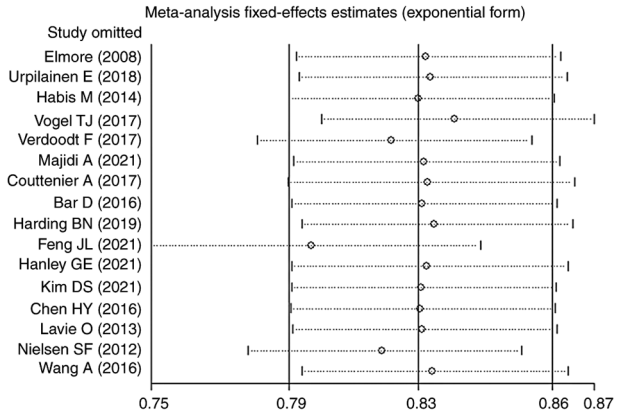

Figure 11. Sensitivity plots for the relationship between statin use and overall survival in patients with ovarian cancer. The circles indicate the study-specific hazard ratio after excluding the listed study; the horizontal dotted lines indicate 95% confidence intervals.

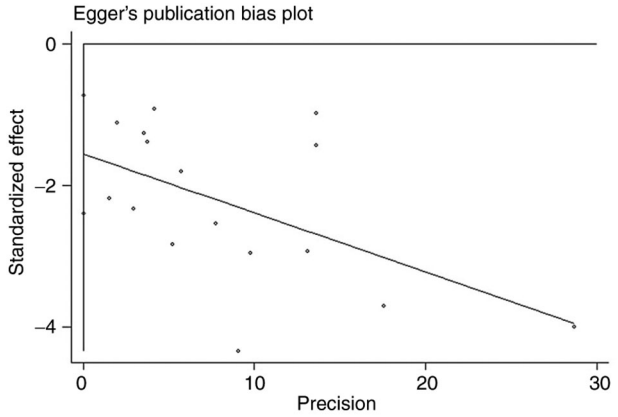

Figure 14. Egger's publication bias plot of the relationship between statin use and overall survival in patients with ovarian cancer. Circles represent the included studies.

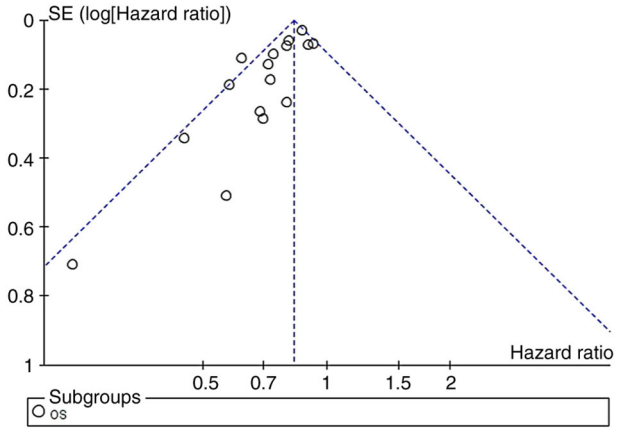

Figure 12. Funnel plot of the relationship between statin use and OS in patients with ovarian cancer. The circles represent the included studies, the x-axis is the effect size, which corresponds to the HR value of each study, the vertical line in the middle of the plot is the combined HR value, and the y-axis is the SE. HR, hazard ratio; OS, overall survival; SE, standard error.

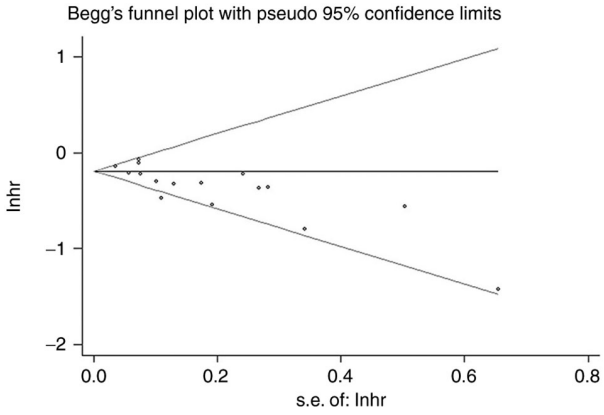

Figure 13. Begg's funnel plot of the relationship between statin use and overall survival in patients with ovarian cancer. Circles represent the included studies. lnhr, Log transformed hazard ratio; s.e., standard error.

multiple endpoints, resulting in the same study being evaluated more than once in a single analysis. Secondly, although the HR data after multifactorial adjustment were combined, numerous confounding factors affecting the prognostic relevance of statin use in OC remained. Thirdly, the duration of statin use and exposure varied across the included studies. The present study did not allow for a specific analysis and conclusion on the duration of statin use, and further large clinical trials are needed to draw any conclusions here. Finally, the present meta-analysis was limited to studies published in English. Therefore, publication bias cannot be excluded.

In conclusion, the use of statins significantly improved the prognosis of patients with OC, especially those with serous and endometrial OC. It is recommended that statins should be prescribed as early as possible after the diagnosis of OC to improve lipid metabolism and prolong patient survival.

Acknowledgements

Not applicable.

Funding

This study was supported by The Key Project Plan of Hebei Province Medical Science Research in 2018 (grant no. 20180013), and the 2020 Hebei Provincial Science and Technology Plan Project (grant no. 20377749D).

Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Authors' contributions

ZZ and JZ received funding, conceived and designed the study, and resolved all differences through discussion. HH, QZ, XW, SC, ZZ and QW performed data extraction, analysis, interpretation and literature review. QW, ZZ and SC performed literature collection, statistical analysis. QW wrote the first draft of the manuscript. JZ revised important intellectual content manuscript. All authors read and approved the final

manuscript. QW and ZZ confirm the authenticity of all the raw data.All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Momenimovahed Z, Tiznobaik A, Taheri S and Salehiniya H: Ovarian cancer in the world: Epidemiology and risk factors. Int J Womens Health 11: 287-299, 2019.
2. Viale PH: The American cancer society's facts & figures: 2020 Edition. J Adv Pract Oncol 11: 135-136, 2020.
3. Xia C, Dong X, Li H, Cao M, Sun D, He S, Yang F, Yan X, Zhang S, Li N and Chen W: Cancer statistics in China and United States, 2022: Profiles, trends, and determinants. Chin Med J (Engl) 135: 584-590, 2022.
4. Delgado-Ortega L, González-Domínguez A, Borrás JM, Oliva-Moreno J, González-Haba E, Menjón S, Pérez P, Vicente D, Cordero L, Jiménez M, *et al*: The economic burden of disease of epithelial ovarian cancer in Spain: The OvarCost study. Eur J Health Econ 20: 135-147, 2019.
5. Orr B and Edwards RP: Diagnosis and treatment of ovarian cancer. Hematol Oncol Clin North Am 32: 943-964, 2018.
6. Kuroki L and Guntupalli SR: Treatment of epithelial ovarian cancer. BMJ 371: m3773, 2020.
7. Purdie DM, Bain CJ, Webb PM, Whiteman DC, Pirozzo S and Green AC: Body size and ovarian cancer: Case-control study and systematic review (Australia). Cancer Causes Control 12: 855-863, 2001.
8. Li YC, Park MJ, Ye SK, Kim CW and Kim YN: Elevated levels of cholesterol-rich lipid rafts in cancer cells are correlated with apoptosis sensitivity induced by cholesterol-depleting agents. Am J Pathol 168: 1107-1118, 1404-1405, 2006.
9. Dulak J and Józkowicz A: Anti-angiogenic and anti-inflammatory effects of statins: Relevance to anti-cancer therapy. Curr Cancer Drug Targets 5: 579-594, 2005.
10. Jakobisiak M and Golab J: Potential antitumor effects of statins (Review). Int J Oncol 23: 1055-1069, 2003.
11. Irvin S, Clarke MA, Trabert B and Wentzensen N: Systematic review and meta-analysis of studies assessing the relationship between statin use and risk of ovarian cancer. Cancer Causes Control 31: 869-879, 2020.
12. Lavie O, Pinchev M, Rennert HS, Segev Y and Rennert G: The effect of statins on risk and survival of gynecological malignancies. Gynecol Oncol 130: 615-619, 2013.
13. Olsen CM, Green AC, Whiteman DC, Sadeghi S, Kolahdooz F and Webb PM: Obesity and the risk of epithelial ovarian cancer: A systematic review and meta-analysis. Eur J Cancer 43: 690-709, 2007.
14. Mohammadian-Hafshejani A, Sherwin CMT and Heidari-Soureshjani S: Do statins play any role in reducing the incidence and mortality of ovarian cancer? A systematic review and meta-analysis. J Prev Med Hyg 61: E331-E339, 2020.
15. Majidi A, Na R, Dixon-Suen S, Jordan SJ and Webb PM: Common medications and survival in women with ovarian cancer: A systematic review and meta-analysis. Gynecol Oncol 157: 678-685, 2020.
16. Li X and Zhou J: Impact of postdiagnostic statin use on ovarian cancer mortality: A systematic review and meta-analysis of observational studies. Br J Clin Pharmacol 84: 1109-1120, 2018.
17. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M and Tugwell P: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, 2010. Available online at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed September 10, 2022.
18. Parmar MK, Torri V and Stewart L: Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 17: 2815-2834, 1998.
19. Irwig L, Macaskill P, Berry G and Glasziou P: Bias in meta-analysis detected by a simple, graphical test. Graphical test is itself biased. BMJ 316: 470-471, 1998.
20. Elmore RG, Ioffe Y, Scoles DR, Karlan BY and Li AJ: Impact of statin therapy on survival in epithelial ovarian cancer. Gynecol Oncol 111: 102-105, 2008.
21. Urpilainen E, Marttila M, Hautakoski A, Arffman M, Sund R, Ilanne-Parikka P, Arima R, Kangaskokko J, Puistola U, Hinkula M and Läärä E: Prognosis of ovarian cancer in women with type 2 diabetes using metformin and other forms of antidiabetic medication or statins: A retrospective cohort study. BMC Cancer 18: 767, 2018.
22. Habis M, Wroblewski K, Bradaric M, Ismail N, Yamada SD, Litchfield L, Lengyel E and Romero IL: Statin therapy is associated with improved survival in patients with non-serous-papillary epithelial ovarian cancer: A retrospective cohort analysis. PLoS One 9: e104521, 2014.
23. Vogel TJ, Goodman MT, Li AJ and Jeon CY: Statin treatment is associated with survival in a nationally representative population of elderly women with epithelial ovarian cancer. Gynecol Oncol 146: 340-345, 2017.
24. Verdoodt F, Kjaer Hansen M, Kjaer SK, Pottegård A, Friis S and Dehlendorff C: Statin use and mortality among ovarian cancer patients: A population-based cohort study. Int J Cancer 141: 279-286, 2017.
25. Majidi A, Na R, Jordan SJ, De Fazio A and Webb PM; OPAL Study Group: Statin use and survival following a diagnosis of ovarian cancer: A prospective observational study. Int J Cancer 148: 1608-1615, 2021.
26. Couttenier A, Lacroix O, Vaes E, Cardwell CR, De Schutter H and Robert A: Statin use is associated with improved survival in ovarian cancer: A retrospective population-based study. PLoS One 12: e0189233, 2017.
27. Bar D, Lavie O, Stein N, Feferkorn I and Shai A: The effect of metabolic comorbidities and commonly used drugs on the prognosis of patients with ovarian cancer. Eur J Obstet Gynecol Reprod Biol 207: 227-231, 2016.
28. Harding BN, Delaney JA, Urban RR and Weiss NS: Use of statin medications following diagnosis in relation to survival among women with ovarian cancer. Cancer Epidemiol Biomarkers Prev 28: 1127-1133, 2019.
29. Feng JL, Dixon-Suen SC, Jordan SJ and Webb PM: Statin use and survival among women with ovarian cancer: An Australian national data-linkage study. Br J Cancer 125: 766-771, 2021.
30. Hanley GE, Kaur P, Berchuck A, Chase A, Grout B, Deurloo CM, Pike M, Richardson J, Terry KL, Webb PM and Pearce CL: Cardiovascular medications and survival in people with ovarian cancer: A population-based cohort study from British Columbia, Canada. Gynecol Oncol 162: 461-468, 2021.
31. Kim DS, Ahn HS and Kim HJ: Statin use and incidence and mortality of breast and gynecology cancer: A cohort study using the national health insurance claims database. Int J Cancer 150: 1156-1165, 2022.
32. Chen HY, Wang Q, Xu QH, Yan L, Gao XF, Lu YH and Wang L: Statin as a combined therapy for advanced-stage ovarian cancer: A propensity score matched analysis. Biomed Res Int 2016: 9125238, 2016.
33. Nielsen SF, Nordestgaard BG and Bojesen SE: Statin use and reduced cancer-related mortality. N Engl J Med 367: 1792-1802, 2012.
34. Wang A, Aragaki AK, Tang JY, Kurian AW, Manson JE, Chlebowski RT, Simon M, Desai P, Wassertheil-Smoller S, Liu S, *et al*: Statin use and all-cancer survival: Prospective results from the women's health initiative. Br J Cancer 115: 129-135, 2016.
35. Surveillance Epidemiology and End Results Program, Ovary Cancer Survival Statistics. http://seer.cancer.gov/statfacts/html/ovary.html2021. Accessed April 21, 2021.
36. Kwan ML, Habel LA, Flick ED, Quesenberry CP and Caan B: Post-diagnosis statin use and breast cancer recurrence in a prospective cohort study of early stage breast cancer survivors. Breast Cancer Res Treat 109: 573-579, 2008.
37. Ahern TP, Pedersen L, Tarp M, Cronin-Fenton DP, Garne JP, Silliman RA, Sørensen HT and Lash TL: Statin prescriptions and breast cancer recurrence risk: A Danish nationwide prospective cohort study. J Natl Cancer Inst 103: 1461-1468, 2011.

38. Cruz PMR, Mo H, McConathy WJ, Sabnis N and Lacko AG: The role of cholesterol metabolism and cholesterol transport in carcinogenesis: A review of scientific findings, relevant to future cancer therapeutics. Front Pharmacol 4: 119, 2013.
39. Zhao J, Zhi Z, Wang C, Xing H, Song G, Yu X, Zhu Y, Wang X, Zhang X and Di Y: Exogenous lipids promote the growth of breast cancer cells via CD36. Oncol Rep 38: 2105-2115, 2017.
40. Camarda R, Zhou AY, Kohnz RA, Balakrishnan S, Mahieu C, Anderton B, Eyob H, Kajimura S, Tward A, Krings G, *et al*: Inhibition of fatty acid oxidation as a therapy for MYC-overexpressing triple-negative breast cancer. Nat Med 22: 427-432, 2016.
41. Liu H, Liang SL, Kumar S, Weyman CM, Liu W and Zhou A: Statins induce apoptosis in ovarian cancer cells through activation of JNK and enhancement of Bim expression. Cancer Chemother Pharmacol 63: 997-1005, 2009.
42. Niemi RJ, Braicu EI, Kulbe H, Koistinen KM, Sehouli J, Puistola U, Mäenpää JU and Hilvo M: Ovarian tumours of different histologic type and clinical stage induce similar changes in lipid metabolism. Br J Cancer 119: 847-854, 2018.
43. Park YH, Jung HH, Ahn JS and Im YH: Statin induces inhibition of triple negative breast cancer (TNBC) cells via PI3K pathway. Biochem Biophys Res Commun 439: 275-279, 2013.
44. Sassano A and Platanias LC: Statins in tumor suppression. Cancer Lett 260: 11-19, 2008.
45. Jiang P, Mukthavaram R, Chao Y, Nomura N, Bharati IS, Fogal V, Pastorino S, Teng D, Cong X, Pingle SC, *et al*: In vitro and in vivo anticancer effects of mevalonate pathway modulation on human cancer cells. Br J Cancer 111: 1562-1571, 2014.
46. Campbell MJ, Esserman LJ, Zhou Y, Shoemaker M, Lobo M, Borman E, Baehner F, Kumar AS, Adduci K, Marx C, *et al*: Breast cancer growth prevention by statins. Cancer Res 66: 8707-8714, 2006.
47. Risch HA: Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. J Natl Cancer Inst 90: 1774-1786, 1998.

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.