Review

Do statins play any role in reducing the incidence and mortality of ovarian cancer? A systematic review and meta-analysis

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Keywords

Statin • Ovarian cancer • Incidence • Mortality

Summary

Introduction. *This systematic review and meta-analysis aimed to investigate the relationship between statin consumption and risk of incidence of ovarian cancer (OC) and associated mortality.*

Methods. *Computerized searches were conducted in three electronic databases (PubMed, Web of Science, and Scopus). Two calibrated authors performed the publications selection, data extraction, and quality assessment of the selected publications. The quality of the included articles was evaluated using the Newcastle-Ottawa Scale (NOS) for observational studies, and Jadad criteria for randomized clinical trials (RCTs). The electronic searches retrieved 2272 titles/abstracts. After the deletion of duplicate publications, 2030 titles/abstracts were assessed. Eighteen articles were included.*

Results. *Meta-analysis demonstrated that risk ratio (RR) of the association between statin consumption and OC incidence was 0.88 (95% CI = 0.75-1.03, P = 0.109). Patients receiving statin were less likely to die than those who did not receive statin, with a statistically significant association [RR = 0.76 (95% CI 0.67-0.86, P = 0.0001)]. There was no evidence of publication bias in examining the association between statin consumption and the risk of incidence and mortality from OC.*

Conclusions. *This study determined that statin use reduced the incidence risk of OC and significantly increased the survival in OC patients.*

Introduction

Ovarian cancer (OC) and its predominant pathological subtype, referred to as epithelial OC, are considered the seventh leading cancer among women worldwide [1]. The incidence of OC was reportedly 24469 cases, of whom 14,008 cases die due to the disease, in the USA (USA) in 2018 [2]. OC imposes a high direct and indirect economic burden on the healthcare system and society [3].

Several risk factors such as genetic predisposition, older age at menopause, breast cancer, hormone replacement therapy (HRT), and environmental and lifestyle factors such as pollutant exposure and smoking are associated with increased incidence of OC [4-6]. Current advances in prevention strategies and molecular mechanisms are being utilized to improve women's health outcomes and quality of life [7].

Several choices of treatment and prevention have so far been investigated to reduce OC in women. Hydroxymethylglutaryl-coenzyme A reductase inhibitor, which is commonly called statin and is a cholesterol-lowering drug, is one of the promising drugs for OC [8]. This drug is widely used to treat and prevent hypercholesterolemia and to reduce the risk of coronary heart disease [9, 10].

Recent studies have reported that statin could reduce the risk of OC incidence [11, 12] and also its post-diagnosis use can improve the survival of OC patients [11, 13-15]. In contrast, some studies have not reported any strong evidence on the protective effect of statins in reducing the risk of incidence [16-18] and mortality from OC [19-21].

Although the protective effects of statins against the onset of certain types of cancers have been proven, contradictory results have been reported by studies on the effects of statins on the incidence and mortality of OC, so that some investigations have considered statins as the protective agents [11, 13, 15], as risk factors [17, 22] and neutral [18, 21, 23]. There is not any definitive conclusion on the effects of Statins on the risk of incidence and mortality of OC. Undoubtedly, the results of meta-analysis studies can be helpful in this regard. Therefore, this meta-analysis aimed to investigate the relationship between statin consumption and risk of OC to correlate the current reports on this association.

Methods

Data sources and search strategy

This meta-analysis was performed in accordance with PRISMA guideline (http://www.prisma-statement.org). An extensive systematic review was done on 15 July 2019

in PubMed, Web of Science (ISI) and Scopus databases. The main and MeSH keywords below were used to conduct the search: ((statin*) or (("hydroxymethylglutaryl-CoA reductase") or ("HMGCoA reductase") and (inhibitor*)) or (anticholesteremic) or (simvastatin) or (rosuvastatin) or (pravastatin) or (atorvastatin) or (fluvastatin) or (cerivastatin) or (pitavastatin) or (lovastatin)) and (ovary) or (ovarian)) and (cancer) or (neoplasms) or (carcinoma) or (tumor) or (malignancy). In addition, manual searches and a search in Google Scholar, up to the first 100 hits, were also conducted. Reference lists of similar studies were explored to find more relevant publications that might not be retrieved by manual searching [24, 25].

Study selection

The studies were entered in the *EndNote X8* (released 8 November 2016, Thomson Reuters), and duplicate publications were identified and deleted by the software. Two researchers independently evaluated the titles and abstracts of the studies based on the predetermined inclusion and exclusion criteria. The full texts of all studies that passed this stage were independently reviewed. If any disagreements existed, consensus was achieved by discussion with the third team member. Studies of various types such as cross-sectional, cohort, case-control, and clinical trials were included in the meta-analysis. The included studies addressed the association between statin consumption and the incidence and mortality from OC. Risk Ratio (RR), Odds Ratio (OR) and Hazard Ratio (HR) of the relationship between statin consumption and the incidence or mortality from OC was given a 95% confidence interval (CI) if it had been presented in the article or was calculable based on the information presented in the publication.

Data extraction and quality assessment

Data were extracted by two individuals independently, and potential inconsistencies were resolved through discussion. From the included articles, the following information was drawn: First author's name, year of publication, country where the study was done, sample size, duration of follow-up, and odds ratio (OR) or risk ratio (RR) of incidence and Hazard Ratio (HR) of mortality from OC with 95% confidence interval (CI). For the quality assessment scale, Newcastle-Ottawa Scale (NOS) was used for observational studies, and Jadad criteria was used to assess the quality of the randomized clinical trials (RCTs). Using NOS, we assessed the studies as at extremely high risk of bias (0 to 3 NOS), high risk of bias (4 to 6), and low risk of bias (7 to 9) [26] and for RCTs the score between of 0 (very poor) and for RCTs, the scores of 0 (extremely poor) and 3 or higher (high quality) were considered to investigate their quality [27].

Statistical analysis

In this meta-analysis, we used the RR to estimate the risk of incidence and morbidity of OC. The effect size of the relationship between statin consumption and incidence and mortality from OC were reported by RR with 95% confidence interval (CI), and a two-tailed $P < 0.05$ was considered significance level. Overall summary estimates were calculated using the inverse variance-weighted random-effects meta-analysis. Individual HR and summary estimates were illustrated graphically as forest plots. Heterogeneity among studies was tested by Cochran's Q test (reported with a χ^2 value and P value, with $P < 0.1$ considered as significance level) and the I^2 statistics [28]. Twelve statistics with values of 25%, 50%, and 75% demonstrated low, moderate, and high levels of heterogeneity, respectively [29].

Based on a priori decisions, subgroup analyses were conducted according to the geographical location (Europe, America, and Asia), study quality (low *vs* high risk), sample size for incidence of OC (≥ 100,000 *vs* < 100,000) and mortality from OC (≥ 1,000 *vs* < 1,000), and type of study (case-control, Cohort and RCTs).

A series of sensitivity analyses were performed to more clearly reveal the sources of statistical heterogeneity between studies, as well as to evaluate the robustness of the findings. First, we aimed to examine the effect of individual studies on the summary estimates, and therefore influence analyses were conducted, in which the pooled estimates are recalculated by omitting one study at a time. Secondly, a meta-regression analysis was conducted to assess differences between subgroups. Publication bias was assessed using Begg's and Egger's tests [30, 31]. $P < 0.05$ was considered significance level. All statistical analyses were performed using Stata 12.0 software (Stata LLC, College Station, TX, USA).

Results

Search results, study characteristics of selected studies

A flowchart of the search strategy is illustrated in Figure 1. In the electronic searches, a total of 2,272 titles/abstracts were retrieved. After deletion of duplicate publications, 2,030 titles/abstracts remained. After studying the titles and abstracts of these articles, 1,758 articles that were not related to our subject were excluded. Moreover, 248 publications were excluded because of being published in non-English language, being review articles, meeting, letter to editor, and in vivo and in vitro studies. In this systematic review and meta-analysis, only studies published since 2000 were evaluated. After the study of the finally enrolled 24 articles, two other studies were excluded because the effect size of statin on the incidence or mortality of OC had not been calculated or not been reported in the study and four studies were found as being irrelevant to my research according to the information of the full texts of the articles. Eighteen articles were selected for final analysis, of which ten articles were included for the assessment of the relationship between statin use and the risk of developing OC [11, 12, 16-18, 22, 23, 32-34], and nine articles for the relationship between post-diagnosis statin consumption and OC mortality [11, 13-15, 19-21, 35, 36]. It should be noted that Lavie et al. study [11], addressed both the risk of incidence and mortality of from OC (Fig. 1).

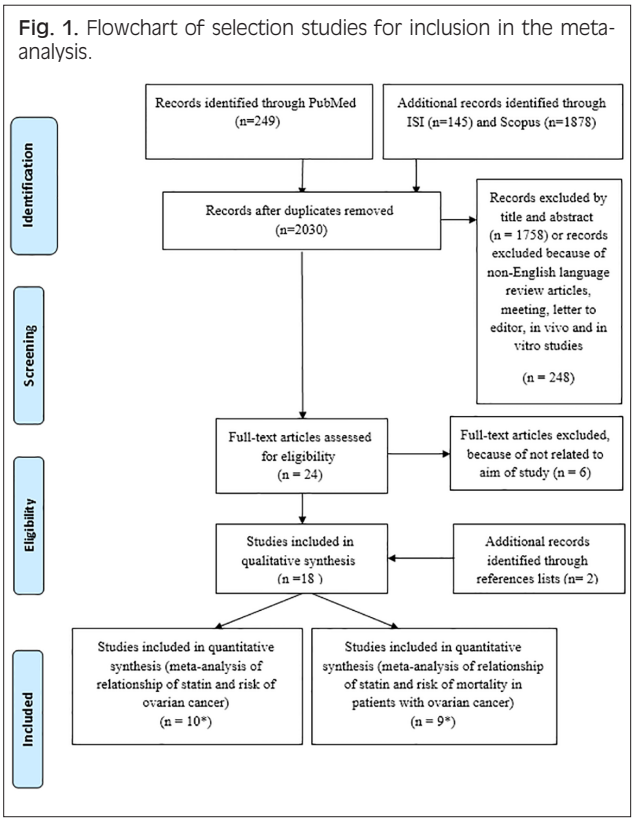


Fig. 1. Flowchart of selection studies for inclusion in the meta-analysis.

Characteristics of selected studies regarding the association between statins consumption and the risk of OC

Based on ten studies, a total of 1,254,501 participants were entered into the study based on the inclusion criteria. There were 7,943 cases of OC incidence reported in the included studies. Among the studies included [11, 12, 16-18, 22, 23, 32-34], four studies were cohort studies with total sample size of 428,613 individuals [17, 22, 33, 34], five studies were case-control with total sample size equal to 82,4891 individuals [11, 12, 16, 18, 32] and one was a clinical trial with total sample size equal to 997 individuals [23]. The reviewed articles had been published between 2001-2018 Six of the included studies were conducted in USA [12, 17, 22, 23, 33, 34], three in Europe [16, 18, 32] and one in Asia [11]. The sample size was 682-748, 282 participants and the mean follow-up of the participants period was 59-130 months (Tab. I).

Statin consumption and the incidence risk of OC

This meta-analysis included ten studies investigating the association between statin consumption and the risk of developing OC [11, 12, 16-18, 22, 23, 32-34]. Adjusted variables in the assessment of the relationship between statin use and risk of OC incidence are shown in Table II. The crude RR of the association between statin consumption and OC incidence is illustrated in Figure 2. People who received statin(s) were less likely to develop OC than those who did not, although the association was not statistically significant (RR = 0.88, 95% CI = 0.75-1.03, P = 0.109).

There was a significant heterogeneity among the results of the meta-analysis (χ^2 = 20.77, df = 9, P = 0.014, I^2 = 56.7%). Sensitivity analysis was performed by excluding studies from analysis one by one at each run. However, the number of pooled RRs did not change significantly, which indicates the robustness of the meta-analysis results (Fig. 2).

Subgroup analysis was performed to determine the association between statin consumption and risk of OC based on study design, sample size, and geographical location. The RR of OC in statin recipients was (RR = 0.82, 95% CI = 0.65-1.03, P = 0.09) in case-control studies; (RR = 0.98, 95% CI = 0.77-1.23, P = 0.848) in cohort studies; and (RR = 0.2, 95% CI = 0.01-4.15, P = 0.298) in clinical trials. Based on an analysis of geographical location, the RR of OC was (RR = 0.88, 95% CI = 0.69-1.12, P = 0.292) in North America; (RR = 0.98, 95% CI = 0.88-1.09, P = 0.732) in Europe; and (RR = 0.49, 95% CI = 0.28-0.81, P = 0.005) in Asia. Moreover, the RR of OC in studies with sample size < 10,000 was (RR = 0.65,

Tab. I. Characteristics of included studies for reviewing the incidence of OC.

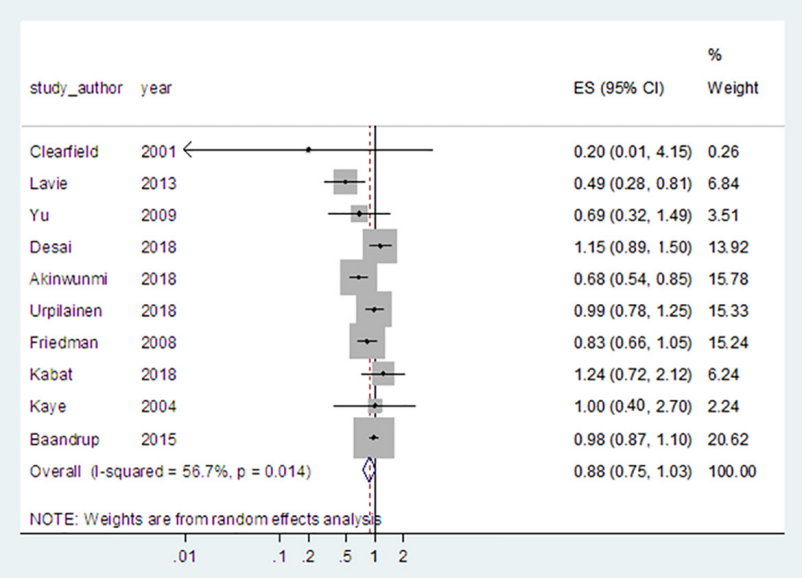
Publication first author	Year	Study setting	Study design	Sample size	Percentage of cancer cases	RR	95 % CI	Study period	Follow-up (median)	NOS
Urpilainen [16]	2018	Finland	Case-control study	748,282	0.04%	0.99	(0.78-1.25)	1996-2011	65	7
Friedman [33]	2008	USA	Cohort	169,261	0.05%	0.83	(0.66-1.05)	1994-2003	59	7
Kabat [17]	2018	USA	Cohort	24,208	0.48%	1.24	(0.72-2.12)	1993-1998	-	6
Kaye [18]	2004	UK	Case-control study	8,978	1.01%	1	(0.4-2.7)	1990-2002	77	8
Baandrup [32]	2015	Denmark	Case-control study	62,809	6.53%	0.98	(0.87-1.10)	2000-2011	-	8
Clearfield [23]	2001	USA	RCT	997	0.20%	0.2	(0.01-4.15)	-	62.4	6*
Lavie [11]	2013	Israel	Case-control study	682	18.48%	0.49	(0.28-0.81)	2003-2010	-	8
Yu [34]	2009	USA	Cohort	73,336	0.44%	0.69	(0.32-1.49)	1990-2004	67	8
Desai [22]	2018	USA	Cohort	161,808	0.47%	1.15	(0.89-1.50)	1993-1998	130	8
Akinwunmi [12]	2018	USA	Case-control study	4,140	49.28%	0.68	(0.54-0.85)	1992-2008	-	8

*: Jadad criteria was applied to assess the quality of the randomized clinical trials.

Tab. II. Adjusted variables in assessment relationship of statin use and risk of incidence of OC.

Publication first author	Year	Adjusted variables
Urpilainen [16]	2018	Age and duration of diabetes medication
Friedman [33]	2008	Calendar year
Kabat [17]	2018	Lipids or insulin
Kaye [18]	2004	Age, smoking, sex, smoking, body mass index (BMI) (kg/m^2)
Baandrup [32]	2015	Duration, intensity, term use
Clearfield [23]	2001	-
Lavie [11]	2013	Age
Yu [34]	2009	Age and BMI at the beginning of the study period, diabetes, high triglyceride and another lipid-lowering drug use, which were treated as time-varying covariates
Desai [22]	2018	Age, BMI, ethnicity, smoking status, education, current medical provider, baseline Hormone Therapy (HT) type and baseline HT duration
Akinwunmi [12]	2018	Age, study center, study phase, BMI, parity, educational status, use of oral contraceptive pills, history of tubal ligation, family history of OC, smoking status, and menopausal status

Fig. 2. Overall analysis of statin use and the incidence of OC.



95% CI = 0.53-0.80, P = 0.0001) and in studies with sample size >10,000 (RR = 0.98 95% CI = 0.90-1.07, P = 0.611) (Tab. III).

Evaluation of publication bias related to statin consumption and the incidence risk of OC

There was no evidence of publication bias in examining the association between statin consumption and the risk of incidence of OC. Therefore, tests of publication bias assessment were not statistically significant (Begg's test, p-value = 0.815; Eggers test, P value = 0.310).

Characteristics of studies in terms of the association between statins intake and risk of mortality in patients with OC

In nine meta-analysis studies, a total of 14,382 participants were enrolled based on our inclusion criteria. Among the included studies [11, 13-15, 19-21, 35, 36], seven studies were cohort with total sample size of 8,630 cases with

Tab. III. Subgroup analysis of the association between statin consumption and the incidence of OC.

Characteristics		Study n.	RR (95%CI)	P-value	Heterogeneity
Study type	RCT	1	0.20 (0.01-4.15)	0.298	0%
	Cohort	5	0.93 (0.78-1.10)	0.414	32.3%
	Case-control	5	0.82 (0.65-1.03)	0.09	72.3%
Study location	North America	7	0.86 (0.72-1.04)	0.122	49.8%
	Europe	3	0.98 (0.88-1.09)	0.73	0%
	Asia	1	0.49 (0.30-0.81)	0.005	0%
Sample size	Less than 10,000	4	0.65 (0.53-0.80)	0.0001	0%
	More than 10,000	7	0.95 (0.87-1.05)	0.330	7.5%

OC [13-15, 19, 20, 35, 36] and two studies were case-control studies with total sample size of 210 cases with OC [11, 21]. The studies had been published between 2008 and 2019. The sample size of recruited participants in the studies ranged was 60-5,416. The mean follow-up of participants was 6-48.8 months. Four of the included studies had been conducted in the USA [14, 15, 35, 36], two in Europe [13, 19] and three in Asia [11, 20, 21] (Tab. IV).

Statin intake and the risk of mortality from OC

This meta-analysis included nine studies that investigated the association between statin consumption and the risk of mortality from OC [11, 13-15, 19-21, 35, 36]. In the reviewed studies, adjusted variables had been included for the assessment of the relationship between statin consumption and the risk of mortality from OC (Tab. V). The crude RR of the association between statin consumption and the risk of mortality from OC is illustrated in Figure 3.

Patients receiving statins had reportedly lower mortality rate compared to those who did not. Notably, this association was statistically significant (RR = 0.76, 95% CI = 0.67-0.86, P = 0.0001) (Fig. 3).

There was a significant heterogeneity among the results of the meta-analysis (χ^2 = 4.19, df = 8, P = 0.077, I^2 = 43.6%). Sensitivity analysis was evaluated by excluding studies from analysis one by one at each run. However, the number of pooled RRs did not change significantly, indicating the robustness of the meta-analysis study results.

Subgroup analysis was done to investigate the association between statin consumption and the risk of mortality from OC based on study design, sample size, and geographical location. The RR of OC in statin recipients was (RR = 0.40, 95% CI = 0.19-0.85, P = 0.017) in case-control studies and (RR = 0.80, 95% CI = 0.74) in cohort studies. For geographical location, the results below were obtained: (RR = 0.70, 95% CI = 0.61-0.80, P = 0.0001) in North America; (RR = 0.84, 95% CI = 0.77-0.93,

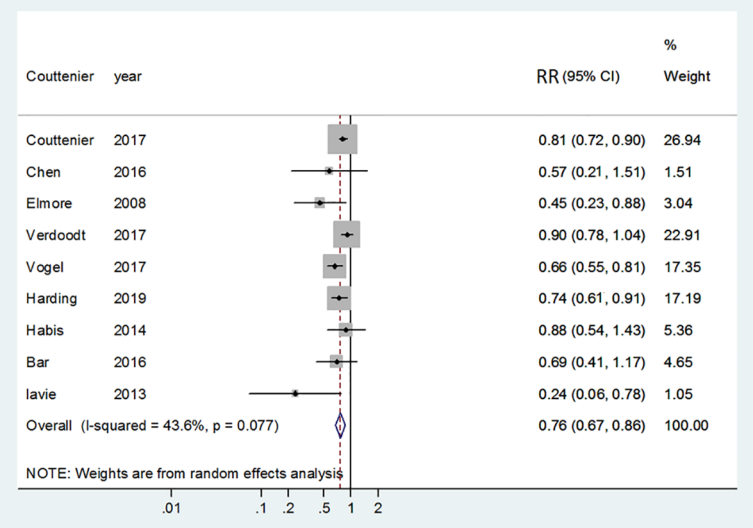
Tab. IV. Characteristics of included studies for survival

Publication first author	Year	Study setting	Study design	Sample size	Percentage of death	RR	95 % CI	Study period	Follow-up (median)	NOS
Couttenier [13]	2017	Belgium	Retrospective cohort	5416	37.64%	0.81	(0.72-90)	2004-2012	6 to 36 months	8
Chen [21]	2016	China	Retrospective	60	36.66%	0.57	(0.21-1.51)	2009-2013	30.3	6
Elmore [15]	2008	USA	Retrospective cohort	126	NA	0.45	(0.23-0.88)	1996-2001	54	7
Verdoodt [19]	2017	Denmark	Prospective cohort	4419	55.30%	0.9	(0.78-1.04)	2000-2013	29	9
Vogel [14]	2017	USA	Retrospective cohort	1431	NA	0.66	(0.55-0.81)	2007-2009	30.6	9
Harding [36]	2019	USA	Prospective cohort	2195	36.00%	0.74	(0.61-0.91)	2007-2012	26.5	8
Habis [35]	2014	USA	Retrospective cohort	442	NA	0.88	(0.54-1.43)	1992-2013	41.6	7
Bar [20]	2016	Israel	Retrospective cohort	143	54.54%	0.69	(0.41-1.17)	2000-2012	48.8	9
Lavie [11]	2013	Israel	Retrospective	150	40.66%	0.24	(0.06-0.78)	2003-2010	34	8

Tab. V. Adjusted variables in assessment relationship of statin use and mortality of OC.

Publication first author	Year	Adjusted variables
Couttenier [13]	2017	Age at diagnosis, year of diagnosis, comorbidities, cancer stage, and cancer treatments
Chen [21]	2016	Age, Federation International de Gynecologic at d'Obstétrique (FIGO) stage, tumor grade, histological subtype, cytoreductive surgery, cycles of chemotherapy, comorbidities (hypercholesterolemia and cardiovascular diseases)
Elmore [15]	2008	Age, diabetes mellitus, grade, stage, suboptimal cytoreduction
Verdoodt [19]	2017	Age at diagnosis, clinical stage, and year of diagnosis, tumour histology, chemotherapy, highest achieved education, disposable income, marital status, non-statin drug use and several comorbidities
Vogel [14]	2017	Age, race, median household income, stage, histology, platinum therapy, Charlson index, heart disease, diabetes, obesity, dyslipidemia
Harding [36]	2019	Age at diagnosis, year at diagnosis, race/ethnicity, marital status, surgical treatment received, grade of disease, stage at diagnosis, census tract poverty level, location of residence, Deyo-Charlson comorbidity score, comorbidities
Habis [35]	2014	Age, race, BMI, smoking status, comorbidities, physical status scores class, surgery characteristics, histologic subtype, FIGO stage, tumor site and grade of disease
Bar [20]	2016	Age, grade of disease, neoadjuvant chemotherapy, beta-blockers, aspirin, metformin, beta-blockers and comorbidity
Lavie [11]	2013	Age

Fig. 3. Overall analysis of statin use and the survival of OC.



Tab. VI. Subgroup analysis of the association between statin consumption and mortality of OC.

Characteristics		Study n.	RR (95%CI)	P-value	Heterogeneity
Study type	RCT	-	-	-	-
	Cohort	7	0.80 (0.74-0.85)	0.0001	38.7%
	Case-control	2	0.40 (0.19-0.85)	0.017	18.6%
Study location	North America	4	0.70 (0.61-0.80)	0.0001	3.7%
	Europe	2	0.84 (0.77-0.93)	0.0001	25%
	Asia	3	0.58 (0.37-0.88)	0.012	22.2%
Sample size	Less than 1,000	5	0.64 (0.48-0.86)	0.003	27.3%
	More than 1,000	4	0.80 (0.74-0.86)	0.0001	54.1%

P = 0.0001) in Europe; and (RR = 0.58, 95% CI = 0.37-0.88, P = 0.012) in Asia.

In addition, the RR related to mortality in OC patients associated with sample size < 1,000 was (RR = 0.64, 95% CI = 0.48-0.86, P = 0.003) and with sample size > 1,000 was (RR = 0.80, 95% CI = 0.74-0.86, P = 0.0001) (Tab. VI).

Evaluation of publication bias related to statin consumption and risk of mortality from OC

There was no evidence of publication bias based on our extensive analysis of the association between statin consumption and the risk of mortality from OC. The results of the analysis for the bias of assay tests were not statistically significant [Begg's test (P = 0.118); Egger's test (P = 0.118)].

Discussion

The purpose of this systematic review and meta-analysis was to investigate the relationship between statin consumption and the risk of OC incidence and survival in the patients. The study indicated that statin consumption reduced the risk of OC incidence by 12%. but given the 95% CI for the calculated RR, this relationship was not statistically significant.

However, statin consumption significantly reduces the risk of mortality in patients with OC. Overall; studies have also indicated that statins have beneficial effects on the prevention of death and incidence in gynecological cancers. Some studies reported that statin consumption could be inversely correlated with OC risk and mortality in gynecological cancers such as OC, endometrial and breast [25, 37-40]. However, some studies did not confirm that statins could have an impact on the risk of developing breast cancer, colorectal cancer, and lung cancer [41].

Statins help to treat hyperlipidemia through inhibiting hepatic cholesterol biosynthesis by blocking the rate-limiting phase in the mevalonate pathway via inhibiting hydroxymethylglutaryl-coenzyme A reductase (HMGCR) in hepatocytes [38]. Besides that, statins have shown anti-tumor activity and produce effect on metastasis formation so that they reduce the risk of cancer via various mechanisms, including increasing apoptosis cancer cell differentiation, activating anti-proliferative and pro-apoptotic signals, inhibiting cancer cell proliferation, modulating p53, p21, caspase 3 and caspase 6, sensitizing tumor cells to NK cell activity, blocking isoprenoids production (which play an important role in post-translational modifications of various proteins) or inhibiting activation of the proteasome pathway, inhibiting reactive oxygen species (ROS) production and inhibiting inflammation. These mechanisms have been discovered by means of cellular assays [38, 40, 41].

Moreover, obesity-related metabolic disorders including hypercholesterolemia can have an adverse effect on the prognosis of some cancers [38]. It should be noted that the effects of statins depend on their dosages (dose-response), duration of exposure of cells to the drug, the individual cell line, and statin type [42]. A meta-analysis showed that although statins were effective in preventing the risk of OC incidence, it did not have a significant effect on other gynecological cancers such as endometrial, cervical and vulvar [25].

However, a cohort study on women with type 2 diabetes showed that there was no relationship between statins or metformin consumption and OC incidence [16]. In another study, Desai et al. reported that pravastatin consumption could increase the risk of OC [22]. In addition, Baandrup et al. reported that statin consumption had no effective impact on reducing the risk of OC incidence [32]. The inconsistencies in the available research findings may be due to different sample size, genetic and demographic differences and regional diversities [43-45].

Similarly, subgroup analysis of the association between statin consumption and the incidence of OC indicated significant association for Asia (RR = 0.49, 95% CI 0.28-0.81, P = 0.005). The results of our meta-analysis demonstrates that patients receiving statins were significantly less likely to have increased risk of mortality compared to those who did not (RR = 0.76, 95% CI = 0.67-0.86, P = 0.0001). In agreement with this study, it has been suggested that long-term statin consumption is beneficial for primary prevention [46].

Other meta-analyses and review articles on gynecological cancers, such as breast and endometrial, have demonstrated that statin consumption generally has substantial survival-related benefits in terms of both disease-specific survival and overall survival, contributing to both pre- and post-diagnosis statin consumption [48-50]. Other meta-analyses have suggested that statin consumption is associated with an increase in survival for lung cancer [50], esophageal cancer [51], pancreatic cancer [52, 53] and endocrine-related gynecologic cancers [54].

A comparably comprehensive systematic review of cancer survival and incidence is one of the strengths of this study. In this study, subgroup analysis was also performed on several variables potentially affecting the incidence and mortality from OC, thereby increasing the power of the study and reliability of results. Most of the reviewed articles were of retrospective observational clinical type. Therefore, the analysis of the published studies may be affected by the available data or selection bias, comorbidity bias, and unmeasured or incomplete variables, as confounding variables, may also have affected the results of our systematic review. Other drugs are also likely to be taken during statin therapy, which might not have been included in the reviewed study, which may be a confounding variable. As mentioned above, simultaneous consumption of statins and other drugs can lead to interactions and even cytotoxic effects [10, 55, 56].

Although statins are mostly considered safe drug for a vast majority of patients, they may develop certain adverse effects including myalgia, rhabdomyolysis, and myopathy in some patients. Statins are known to interact with some cytochrome p450 enzyme groups [10].

There are few clinical trials on the effect of statins on the incidence and mortality of OC, and given the role of these studies in determining the therapeutic effects of drugs, it is recommended that multicenter randomized clinical trials studies with a large sample size be performed worldwide, so that we can use the results of these studies to make appropriate therapeutic decisions. Therefore, in order to obtain more reliable results, further trials should be carried out on cancer incidence and mortality. In addition, given the limited number of studies on this subject, we have only performed subgroup analysis based on geographical location, type of study, and sample size. Therefore, in this study, it was not possible to perform subgroup analysis based on other variables such as gender, age groups, duration of treatment with statins and drug type. Most studies have been conducted in the US and Europe, and no study has yet been conducted in Africa.

Conclusions

Given the lack of consensus on this subject and the relationship between statin consumption and ovarian cancer, this systematic review and meta-analysis robustly demonstrates that statin consumption can reduce the risk of OC incidence are by 12%, but the association is not statistically significant. Importantly, statin consumption was found to significantly increase the rate of survival in patients with OC. Therefore, statins may serve as a promising adjunctive anticancer drug for the prevention and reduction of mortality from OC. However, further clinical trials should be conducted to assess this relationship and its potential contribution to improving health outcomes for women at risk of OC.

Acknowledgements

Funding sources: this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

All authors contributed to the design of the review. SHS and AMH extracted and summarized the data. All authors contributed to drafting the manuscript. SHS,

CMS and AMH edited the first draft. Finally, all authors reviewed, commented, and approved the final draft.

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Received on March 10, 2020. Accepted on May 18, 2020.

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How to cite this article: Mohammadian-Hafshejani A, Sherwin CMT, 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 2020;61:E331-E339. https://doi.org/10.15167/2421-4248/jpmh2020.61.3.1497