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Systematic review and meta-analysis of studies assessing the relationship between statin use and risk of ovarian cancer

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Abstract

Purpose: The link between lipid-stabilizing medications and epithelial ovarian carcinogenesis is incompletely understood. Statins may reduce ovarian cancer risk, but results are inconclusive.

Methods: We conducted a systematic review and meta-analysis of studies reporting associations between statin use and ovarian cancer risk in PubMed. Summary risk ratios (RRs) and confidence intervals (CIs) were calculated. Subgroup analyses by cancer histotype, statin class (lipo- or hydrophilic) and duration of statin use were conducted. Use of individual statins in populations was assessed to determine population-specific differences in statin types.

Results: Nine studies with 435,237 total women were included (1 Randomized controlled trial (RCT); 4 prospective; 4; case-control). Statin use was associated with a reduced risk of ovarian cancer (RR 0.87, 95% CI: 0.74–1.03) and risk was significantly reduced in populations with low pravastatin use (RR 0.83, 95% CI: 0.70–0.99). Risk estimates varied by statin class (3 studies; lipophilic: RR 0.88, 95% CI: 0.69–1.12; hydrophilic: RR 1.06, 95% CI: 0.72–1.57) and cancer histotype (3 studies; serous: RR 0.95, 95% CI: 0.69–1.30; clear cell: RR 1.17, 95% CI: 0.74–1.86). Long-term use was associated with a reduced risk of ovarian cancer (RR 0.77, 95% CI: 0.54–1.10) that further reduced when pravastatin use was low (RR 0.68, 95% CI: 0.46–1.01). Between-study heterogeneity was high overall and in subgroups ($I^2 > 60\%$).

Conclusion: Statins may be associated with a reduced risk of ovarian cancer, but the effect likely differs by individual statin, duration of use and cancer histotype. Additional well-powered studies are needed to elucidate important subgroup effects.

Keywords

ovarian cancer risk; statin; Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors; lipophilic; hydrophilic; histology; review

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Introduction

Ovarian cancer is the most fatal gynecologic malignancy worldwide with estimates of over 295,000 incident cases and >184,000 deaths occurring in 2018 [1]. Currently, no effective screening approaches exist for detecting ovarian cancers [2, 3]. Lack of symptoms early in the disease process leads to >70% of cases identified at a late stage, when 5-year survival estimates are only 30% [4].

The lack of effective screening for early detection of ovarian cancer has fueled extensive study of hormonal and reproductive risk factors. Parity, oral contraceptive use, and tubal ligation decrease risk, while early age at menarche, late menopause, endometriosis and pelvic inflammatory disease increase risk. Recent evidence also suggests that risk factor associations differ by histotype [5–7]. An emerging theory of ovarian cancer carcinogenesis proposes that alterations in lipid metabolism and subsequent inflammation may promote development of some ovarian cancers [5, 8]. Cancer cells have altered cellular metabolism to support dramatically increased cellular proliferation and to adapt to hypoxia [9, 10]. Alterations in lipid metabolism exhibited by ovarian cancer cells include increased production of fatty acids, which help to form cell membranes and perform crucial intra- and intercellular signaling functions - two activities that are essential for dramatic tumor cell propagation [11]. Alterations in the production of lipids can induce inflammation, a condition that has been demonstrated to influence the development of ovarian cancer [12–17]. Inflammation may promote tumor cell proliferation through several pathways, including altered metabolism of tumor-associated necrosis factors) for increased cytokine production and inhibition of Th17 helper cells which suppress T-regulatory (Treg) cells [9].

Because of the link between lipid instability and inflammation, medications that target these pathways may be associated with a reduced risk of incident ovarian cancer [18]. Statins are a group of hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors that are designed to block the formation of mevalonate in the liver- a key component in the formation of cholesterol [19]. Statins are lipid-stabilizers designed to lower cholesterol but may also decrease inflammation and alter lipid profiles through multiple HMG-CoA-dependent or independent mechanisms [19–23]. Seven statins are currently available by prescription in the United States, and the prevalence of statin use was 26% in the 2011–2012 NHANES data cycle [24]. Prescription rates vary by geographic location and health plan [25, 26], but in general, statins in the lipophilic drug class are prescribed more frequently than hydrophilic statins [26]. The class of a statin drug is defined by its pharmacokinetic behavior; lipophilic (simvastatin, atorvastatin, lovastatin, fluvastatin and cerivastatin) and hydrophilic statins (pravastatin, rosuvastatin) access cells differently, and may have different pleiotropic effects external to the liver [27, 28].

Recent evidence has suggested that statins may exhibit a protective effect on the development of ovarian cancer [29–32], but power to detect associations in individual studies is limited, and the biological mechanism(s) by which statins may exert their effects on cancer development are not well-understood [33]. Evidence from two recent systematic reviews is conflicting; importantly, neither evaluated ovarian cancer histotype-specific associations, or associations for different classes of statins [34, 35]. We hypothesized that

the effect of statin use on ovarian cancer risk would be heterogenous across cancer histotype, similar to many ovarian cancer risk factors [7], and that risk would also vary by statin lipophilicity. We conducted a systematic review and meta-analysis to assess the association between statin use and ovarian cancer risk that considered both heterogeneity in effects by ovarian cancer histotype and statin class.

Methods

Study identification and inclusion criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to conduct this systematic review and meta-analysis (Figure S1) [36]. A comprehensive search algorithm was developed and utilized to search the PubMed database for all peer-reviewed studies reporting associations between statin use and incident epithelial ovarian cancer. The search was conducted on March 20, 2019. The search algorithm was as follows:

((("hydroxymethylglutaryl-coa reductase inhibitors"[Pharmacological Action] OR "hydroxymethylglutaryl-coa reductase inhibitors" OR ("hydroxymethylglutaryl-coa" AND "reductase" AND "inhibitors") OR "hydroxymethylglutaryl-coa reductase inhibitors" OR "statin") AND ovarian) AND ("neoplasms" OR "neoplasm" OR "cancer"))

This review used no date restriction and no language or geographic restrictions were applied. Eligible studies for this review included all randomized controlled trials (RCTs) and observational studies that reported a risk estimate for ovarian cancer after exposure to statins. Estimates that quantified risk included risk ratios (RR), hazard ratios (HR) or odds ratios (OR) and their corresponding 95% confidence intervals.

All titles and abstracts returned by the search string were scanned to determine eligibility. Full texts of articles passing the initial title and abstract review were scanned for potential inclusion. Reference lists of primary analyses were scanned for additional articles, as were reference lists for all review articles returned by the search string. Any articles referencing overlapping or duplicate populations were first evaluated separately, and the article with the most recent publication date was selected for inclusion.

Data abstraction

Information abstracted from each article included study type (RCT, case-control, cohort or cross-sectional), data source and population characteristics (counts of case subjects and controls/cohort members, geography, time of case, control or cohort ascertainment) and prevalence of statin use by class in the study population. Risk estimates reported for ovarian cancer were abstracted from each study along with their 95% confidence intervals, and included overall, histotype-specific, duration, class of statin, and indication where this information was available.

The Newcastle-Ottawa Scale (NOS) was used to assess bias for the observational studies included in this systematic review based on guidance provided from the Cochrane Handbook

for Systematic Reviews and for comparability to the original systematic review on this topic [37]. Bias was assessed in the randomized controlled trial using Cochrane guidelines.

Meta-analyses

We conducted a random-effects (RE) meta-analysis of the association between statin use and incident ovarian cancer risk across all studies that reported a risk estimate of interest (RR, HR or OR). Because ovarian cancer is a rare outcome, each of these measures is considered an approximation of the RR [34, 38] and were comparable across study type. We visually analyzed study-specific effect estimates with forest plots ordered by both study publication date and by the ascertainment window of exposure in each study. Summary effect estimates with corresponding confidence intervals were generated by RE meta-analysis. Heterogeneity across studies was assessed by I^2 . Subgroup analyses were performed for statin class defined by lipophilicity (hydrophilic or lipophilic) and among women who used statins long-term 5 years.

Additionally, we explored the proportion of individual statins in each study population among the total number of individuals taking a statin drug. We recorded the percentage of each statin used when it was reported by the authors. For any study that did not explicitly report the proportion of each statin, prevalence estimates of statin use during the exposure window and in the geographic location for subjects in that study were obtained from nationally representative or health-plan representative database reports, where applicable. A qualitative categorization was created based on the distribution of percentages across studies and assigned to each statin per study (low 10%, moderate >10%–30%, and high >30%) with percentages based on the frequency of individual statins among all statins used. We performed a sensitivity analysis removing any study that contained moderate or high proportions of statin use in proportion to the total number of individuals exposed to statins in a study to assess the effect of high statin-specific use on the summary estimate. Finally, we performed an analysis of ovarian cancer histotype-specific estimates and produced meta-analyses for all histotypes with 3 studies. All analyses were performed using R version 3.5.3.

Results

Prisma and overview

The PubMed search returned a total of 98 records. The PRISMA flow diagram is presented in Figure S1. A primary reviewer (SI) conducted the systematic review and it was corroborated by a second reviewer (NW). No additional records were identified from reference lists. Two duplicate records were identified: a thesis document that was the basis for one of the included studies [39] was excluded in lieu of the peer-reviewed article. The second duplicate record was determined to be an identical population to another article included in this review [30], and the more recent publication was chosen for inclusion. A total of 96 records were scanned for inclusion. After title and abstract review, 73 studies were excluded. Full texts of the 23 remaining studies were evaluated and 14 were excluded. Reasons for exclusion were: incorrect outcome (n=7), studies conducted on cell lines (n=3), a letter to the editor with no primary data (n=1), and qualitative reviews with no primary

data (n=3). The three review papers did not provide additional studies for inclusion from their reference lists. Nine studies were thus identified that reported primary estimates of incident epithelial ovarian cancer risk after use of statin drugs for inclusion in this review.

Studies included

Studies included one RCT, four cohort studies, and four case-control studies. Five studies were included in the systematic review completed in 2014 [30–32, 40, 41], and four studies were recently published [29, 39, 42, 43] (Table 1). Two were estimates from cohorts: The Women's Health Initiative (WHI) and a registry study of the population of patients with diabetes across Finland in the FinDM database [42, 43]. The remaining two studies were a case-control study from New England (NEC) and a registry-based study conducted in the Danish registry data [29, 39]. Five studies were from US populations and one study from each of four additional countries (Denmark, Finland, Israel and the United Kingdom). Six studies ascertained statin use from prescription records [30–32, 39, 40, 43], and two utilized self-report [29, 42]. There was a total of 357,515 women included across the four cohort studies (n=1,471 incident ovarian cancers), 76,725 women from four case-control studies (n=6,360 cases, n=70,365 controls) and 997 women from the RCT (n=2 incident ovarian cancers) for a total of 435,237 women of which 7,833 were diagnosed with ovarian cancer.

Results of the bias assessment for each study are presented in Table S1. Each observational study was rated on the Newcastle-Ottawa 9-point scale. Two case-control studies [30, 32] did not report whether controls were selected from an at-risk population (i.e., women without history of oophorectomy). The remaining case-control and cohort studies scored 6 on the 9-point scale (Table S1). Our assessment of bias in the randomized controlled trial [41] was determined to be low.

Association of statin use with ovarian cancer

Ever-use of statins were associated with a reduced risk of ovarian cancer across the nine included studies (RR 0.87, 95% CI: 0.74–1.03) (Figure 1). Notably, only one study showed an increased risk of ovarian cancer (Desai) while all others showed a decreased risk or a null association. Heterogeneity was moderate ($I^2=59.3\%$, $p=0.02$). The risk of ovarian cancer after exposure to lipophilic statins (simvastatin, atorvastatin, lovastatin, fluvastatin or cerivastatin) was reduced (RR 0.88, 95% CI: 0.69–1.12) while risk was higher after hydrophilic statin (pravastatin, rosuvastatin) use (RR 1.06, 95% CI: 0.72–1.57; subgroup heterogeneity: $p=0.42$) (Figure 2). Moderate heterogeneity was observed across the three studies included in the lipophilic group ($I^2=74.3\%$, $p=0.02$) and in the hydrophilic group ($I^2=60.5\%$, $p=0.10$).

Six studies reported on the association of ovarian cancer risk with exposure to long-term statin use. Five of the 6 studies defined long-term use as ≥ 5 years of use, and one study reported long-term use as ≥ 3 years [42]. Long-term use was associated with a reduction in risk of ovarian cancer (RR 0.77, 95% CI: 0.54–1.10) across all six studies. In a sensitivity analysis removing the study that defined long-term use as ≥ 3 years, the effect estimate was further reduced (RR 0.68, 95% CI: 0.46–1.01) (Figure 3).

One study evaluated the risk of ovarian cancer after statin use by categories of statin indication, reporting that patients without diabetes (RR 0.63, 95% CI: 0.50–0.80), non-obese individuals (RR 0.56, 95% CI: 0.43–0.74), patients without hypertension (RR 0.63, 95% CI: 0.47–0.86) and those without coronary artery disease (RR 0.68, 95% CI: 0.53–0.86) all had reduced risks of ovarian cancer after use of statins. This study also reported that joint use of statins and aspirin may significantly reduce risk (RR 0.55, 95% CI: 0.38–0.82) [29].

In a subgroup analysis by study design, the risk of ovarian cancer in case-control studies was reduced (OR 0.78, 95% CI: 0.58–1.07) compared to prospective cohort studies (RR 0.96, 95% CI: 0.81–1.14, $p_{\text{int}} = 0.27$) (Figure S2). Six of eight observational studies captured statin use from prescription records (RR 0.94, 95% CI: 0.86–1.03), and two studies relied on patient self-report (Figure S3).

Assessment of individual statins

A review of individual statin prescriptions across studies indicated that simvastatin, atorvastatin and lovastatin were used most frequently in each study population, which was reflective of general prescribing trends [26, 44–46]. Qualitative comparison of statin prescriptions for individual statins (low, moderate, high) showed that the distribution of statin use differed in only one study from the WHI [42] (Table S2). Pravastatin was used by 22.1% of the women in WHI and this frequency was higher than the 8 other studies with estimates below 10%. Statin-specific risk estimates were also reported for the WHI women, and risk of ovarian cancer after use of pravastatin was elevated in models that allowed statin use to vary by time (RR 1.89, 95% CI: 1.24–2.88). Statin use was also associated with ovarian cancer risk overall (RR 1.30, 95% CI: 1.04–1.62) and for hydrophilic statin use (RR 1.72, 95% CI: 1.15–2.56) in this study. A meta-analysis removing the WHI study showed that statin use was associated with a lower risk of ovarian cancer (RR 0.83, 95% CI: 0.70–0.99) (Figure 1).

Association of statin use with ovarian cancer histotypes

Three studies included histotype-specific risk estimates for serous and clear cell tumors (Table 2). Risk of serous ovarian cancer was reduced in the NEC after use of statins (RR 0.69, 95% CI: 0.53–0.90) [29]. An association between statin use with risk of serous ovarian cancer was not observed in WHI (HR 1.22, 95% CI: 0.87–1.70) [42] or in the Danish National Registry data (RR 1.03, 95% CI: 0.90–1.19) [39] (Table 2). A random effects meta-analysis of the three estimates reported for serous tumors was null (RR 0.95, 95% CI: 0.69–1.30) and heterogeneity across studies was high ($I^2=80.4\%$, $p_{\text{het}}=0.01$). Clear cell tumors showed inconsistent effects, and a random-effects meta-analysis was null (RR 1.17, 95% CI: 0.74–1.86, $I^2=39\%$, $p_{\text{het}}=0.19$) (Figure 4).

Two studies reported risk estimates for mucinous and endometrioid tumors. In NEC, statins were associated with a reduced risk of mucinous ovarian cancer (RR 0.39, 95% CI: 0.18–0.82). Statins were also associated with a reduced risk of mucinous tumors for those initiating use below age 60 (RR 0.32, 95% CI: 0.11–0.89) and for statin use less than 5 years duration (RR 0.30, 95% CI: 0.11–0.85) [29]. Statins also reduced the risk of mucinous tumors in the Danish registry data for (RR 0.63, 95% CI: 0.39–1.00) and were associated

with a decreased risk for those who used statins for less than 5 years (RR 0.57, 95% CI: 0.33–0.96) [39]. Risk of endometrioid tumors was reduced for ever vs. never use, 5 or <5 years duration and 60 or >60 years of age at initiation in both the NEC and the Danish registry data. No study evaluated the risk of ovarian cancer histotypes by individual statin (Table 2).

Discussion

We conducted a systematic review and meta-analysis of the association between statin use and risk of invasive epithelial ovarian cancer. Overall, statin use was associated with a reduced, albeit not statistically significant, risk of ovarian cancer (RR 0.87, 95% CI: 0.74–1.03). Ever use of statins was associated with a decreased risk of ovarian cancer in populations where pravastatin use was low (<10%). Long-term statin use was associated with a reduced risk of ovarian cancer across studies assessing the relationship between statin use for three or more years, and the effect was further reduced when limiting to studies that assessed statin use five years or more. The association of ever statin use with ovarian cancer after exposure to lipophilic statins was reduced in comparison to ever use of hydrophilic statins. Reduced risks of mucinous and endometrioid tumors were consistent in the two studies that reported estimates for these histotypes, but risks of serous and clear cell tumors were mixed.

The current systematic review and meta-analysis expands on two previous systematic reviews [34, 47] by incorporating subgroup analyses by statin class, individual statin and histotype of ovarian cancer. An original systematic review on statin use and ovarian cancer risk from 2014 included five studies and reported two meta-analyzed estimates for ovarian cancer risk 1) across all studies and 2) in three studies that reported risk estimates after duration of statin use five years or more. The second review, conducted in 2019, included five additional studies, two of which were from the same WHI population [42, 48]. The 2019 review included non-informative subgroup analyses without consideration for ovarian cancer histology and individual statin characteristics. In contrast, we evaluated pertinent subgroup effects that have not been described previously. We present the first meta-analyzed estimates for risk of ovarian cancer by statin class (lipo- or hydrophilic) and histotypes of ovarian cancer and highlight the added complexity of associations across these subgroups. For example, we used the frequencies of specific statins in each of our populations to show that the association between statins and ovarian cancer risk may be heterogenous by individual statin.

Our findings suggest that risk estimates differed by statin class. The association between ever-users of lipophilic statins and risk of ovarian cancer was reduced compared to the risk for ever-users of hydrophilic statins in three studies reporting class-specific effects. Existing literature suggests that statin classes influence cancer risk in ways that depend on drug properties like bioavailability and transport requirements for the statin compounds across phospholipid membranes of different cell types [28, 49, 50].

Our histotype-specific observations were reflective of recent literature suggesting that ovarian cancer risk factor profiles are heterogenous by tumor histology [7]. Three studies

reported histotype-specific effects and we saw consistently reduced risks of mucinous and endometrioid tumors after ever-use of statins, but inconsistent effects for serous and clear cell tumors. Evidence from large consortia studies of ovarian cancer have suggested that inflammatory conditions like endometriosis [16] and obesity [15] may increase risk of endometrioid tumors, and that smoking [51] may increase risk of mucinous tumors. The lipid-stabilizing and anti-inflammatory properties of statins may contribute to the risk reductions we observed by counteracting tumor-promoting effects of the risk factors.

A central finding of our review is that pravastatin may be associated with increased ovarian cancer risk [28]. We observed a reduced risk of ovarian cancer for ever-users of statins after removal of a study with moderate pravastatin use and in which over 20% of the study population was more than seventy years. Our finding is important, because multiple randomized controlled trials have demonstrated that pravastatin may be positively associated with increased cancer risk particularly in the elderly [52, 53]. It has been proposed that pravastatin use may be associated with cancer risk because it is unable to block the mevalonate synthesis in tissues outside the liver [28]. Multiple theories exist regarding the role of the mevalonate pathway in tumorigenesis, including increased cell proliferation due to increased availability of cholesterol and regulation of cellular energy [54]. Hydrophilic pravastatin is less likely to move through cellular membranes in extrahepatic tissues due to a lack of a sodium-independent bile-acid transporter that is necessary for its transport across cell membranes [55]. Pravastatin is only able to block the mevalonate pathway in the liver itself, and a subsequent up-regulation in mevalonate synthesis may result in extra-hepatic tissues to accommodate the decrease in cholesterol synthesis by the liver [28]. Up-regulation of the mevalonate pathway has been demonstrated in breast, liver, pancreatic and prostate cancers, as well as leukemia and lymphoma [33], and in some studies of epithelial ovarian cancer cells [56, 57]. Lipophilic statins, however, move more freely and can block the mevalonate pathway in tissues outside of the liver while simultaneously inhibiting this pathway intra-hepatically.

Our study has several strengths. We conducted a rigorous systematic literature review that included over 7,000 ovarian cancer cases and performed multiple novel analyses to elucidate the effect of statins on ovarian cancer. We evaluated the effect of individual statins on risk of ovarian cancer by analyzing study-specific statin distributions and identifying a study that contained higher than expected levels of pravastatin. We quantitatively evaluated histotype-specific associations and associations by statin class. A bias assessment determined that the risk of bias in the included studies was low.

Although we were able to provide critical information in our overall and subgroup analyses, we acknowledge that we were limited by the low number of studies that reported risk of incident ovarian cancer. For this reason, some sub-analyses had few studies in each group, and heterogeneity across studies was high. In our overall analysis, we saw a reduced risk of ovarian cancer which was not statistically significant, and we cannot rule out the possibility of a result due to chance. We were not able to conduct meta-analyses for mucinous or endometrioid histotypes due to limited reports of histotype-specific estimates in those groups. Heterogeneity of model adjustment factors was observed across studies attributed to improving knowledge of ovarian cancer risk factors. Most studies reported study-specific

distributions of individual statins, but for three studies, we relied on additional literature sources to gather these distributions with the expectation that the literature provided accurate population-specific estimates.

In summary, we show that all statins may not contribute to ovarian cancer risk in the same manner. Our results, in context with existing literature, signal that more research in robust datasets is needed to elucidate subgroup effects. Future studies should continue to explore associations by cancer histotype and consider statin class as an imperative subgroup effect.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

RR	Risk ratio
OR	odds ratio
CI	confidence interval
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
NEC	New England Case-Control study
NOS	Newcastle-Ottawa Scale

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Figure 1.
Random effects meta-analysis for the association between ever-use of statins with risk of ovarian cancer in the full (n=9) study set, and after removing the Desai study (n=8).

*Effect estimate for Desai 2018 is the non-time dependent association between statin use and ovarian cancer risk in the WHI

Figure 2.
 Association of statin use with risk of ovarian cancer in subgroups defined by statin class (lipo- or hydrophilic)
 *Effect estimate for Desai 2018 is the non-time dependent association between statin use and ovarian cancer risk in the WHI

Figure 3.
Random Effects Meta-Analysis for the Association between long-term statin use and risk of ovarian cancer
*Effect estimate for Desai 2018 is the non-time dependent association between statin use and ovarian cancer risk in the WHI

Figure 4.
Association of statin use with risk of serous and clear cell ovarian cancer

Table 1.
Review of existing literature reporting the association of statin use with ovarian cancer risk

Authors	Time	Data Source	Assessment of statin use	Length of follow-up	Number of Cases	Matching	Control number or baseline cohort size	Association measure (Overall)	Association Measure (Histotype-Specific)
Randomized controlled trials (RCTs) assessing the association of statin use with ovarian cancer									
Clearfield et al. 2001[41]	1990	The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS)	-	5.2 years	2	-	997	Ever use: RR 0.20 (0.01–4.15)	
Cohort studies assessing the association of statin use with ovarian cancer									
Desai et al. 2018[42]	1993–2012	Women's Health Initiative (WHI)	Self-report	9 years	763	-	126,253	Time-Dependent use: HR 1.30 (1.04–1.62) Baseline use: HR 1.15 (0.89–1.50)	Serous: HR 1.22 (0.87–1.70) Clear Cell: HR 1.39 (0.70–2.79)
Yu et al. 2009[31]	1990–2004	Group Health of Washington State	Prescription records	14 years	326	-	93,619	Ever use: HR 0.69 (0.32–1.49)	
Friedman et al. 2008[40]	1994–2003	Kaiser Permanente Medical Care Program Northern California (CPMCP)	Prescription records	>9 years	79	-	NR	Time-dependent use: RR 0.83 (0.66–1.05)	
Urpilainen et al. 2018[43]	1996–2011	Finland Diabetes Database (FinDM)	Prescription records	15 years	303	-	137,643	Ever use: HR 0.99 (0.78–1.25)	
Case-control studies assessing the association of statin use with ovarian cancer									
Baandrup et al. 2015[39]	2000–2011	Danish Cancer Registry	Prescription records	-	4,103	Age	58,706	Ever use: OR 0.98 (0.87–1.10)	Serous: OR 1.03 (0.90–1.19) Endometrioid: OR 0.80 (0.58–1.10) Mucinous: OR 0.63 (0.39–1.00) Clear: OR 1.48 (0.92–2.38)
Lavie et al. 2013 [30]	2003–2010	Hiafa Case-Control study; CITOUS	Prescription records	-	126	Birthyear, residence, ethnicity	126	>1 year use: OR 0.56 (0.33–0.94)	
Akinwunmi et al. 2019[29]	1992–1998–2002–2003–2008	New England Case-Control study (NEC)	Self-report	-	2,040	Age, region of residence	4,140	Ever use: OR 0.65 (0.52–0.82)	Serous: OR 0.69 (0.53–0.90) Endometrioid: OR 0.70 (0.45–1.09) Mucinous: OR 0.39 (0.18–0.82) Clear cell: OR

Authors	Time	Data Source	Assessment of statin use	Length of follow-up	Number of Cases	Matching	Control number or baseline cohort size	Association measure (Overall)	Association Measure (Histotype-Specific)
Kaye and Jick 2004[32]	1990–2002	General Practice Research Database (GPRD)	Prescription records	-	91	Birthyear, sex, general practice, index date, GPRD date of entry	7,393	Current use: RR 1.0(0.4–2.70)	0.67 (0.32–1.38)

Abbreviations: OR= Odds ratio; RR= Relative Risk; HR = Hazard Ratio, NR = Not Reported

Table 2.

Ovarian cancer histotype-specific estimates by study

	Akinwunmi OR (95%CI)	Baandrup OR (95%CI)	Desai OR (95%CI)
<i>Histotype (ever vs. never use)</i>			
Serous	0.69 (0.53–0.90)	1.03 (0.90–1.19)	1.22 (0.87–1.70)
Endometrioid	0.70 (0.45–1.09)	0.80 (0.58–1.10)	-
Mucinous ^a	0.39 (0.18–0.82)	0.63 (0.39–1.00)	-
Clear cell	0.67 (0.32–1.38)	1.48 (0.92–2.38)	1.39 (0.70–2.79)
<i>Histotype (5 years use)</i>			
Serous	0.67 (0.45–0.97)	1.11 (0.88–1.40)	-
Endometrioids	0.69 (0.35–1.35)	0.57 (0.31–1.07)	-
Mucinous ^a	0.56 (0.20–1.60)	0.85 (0.39–1.83)	-
Clear cell	0.61 (0.21–1.80)	2.05 (0.98–4.29)	-
<i>Histotype (< 5 years use)</i>			
Serous	0.72 (0.52–0.99)	1.01 (0.87–1.18)	-
Endometrioid	0.72 (0.42–1.25)	0.88 (0.62–1.24)	-
Mucinous ^a	0.30 (0.11–0.85)	0.57 (0.33–0.96)	-
Clear cell	0.70 (0.29–1.73)	1.32 (0.77–2.24)	-
<i>Histotype (initiation age 60)</i>			
Serous	0.63 (0.44–0.91)	-	-
Endometrioid	0.61 (0.31–1.22)	-	-
Mucinous ^a	0.51 (0.18–1.46)	-	-
Clear cell	0.27 (0.06–1.16)	-	-
<i>Histotype (initiation < age 60)</i>			
Serous	0.76 (0.55–1.07)	-	-
Endometrioid	0.78 (0.45–1.33)	-	-
Mucinous ^a	0.32 (0.11–0.89)	-	-
Clear cell	1.01 (0.46–2.25)	-	-

^aEstimates for mucinous tumors from Akinwunmi paper include borderline mucinous