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Review

Effect of statin on risk of gynecologic cancers: A meta-analysis of observational studies and randomized controlled trials

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HIGHLIGHTS

- We aimed to evaluate the effect of statin on risk of gynecologic cancers.
- Statin use was inverse associated with ovarian cancer risk.
- The protective effect of statin use on endometrial and cervix cancer is suggestive.

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ABSTRACT

Objective. Epidemiologic and clinical findings are inconsistent concerning the risk for gynecologic cancers associated with statin use. We conducted a detailed meta-analysis of all relevant original studies to evaluate the effects of statin on the risk of gynecologic cancers.
Methods. We searched PubMed, Embase, and Cochrane library databases up to February 2014 looking for eligible studies. Summary relative risk (RR) estimates and 95% confidence intervals (CIs) were used to calculate the risk using random-effects models.
Results. A total of 14 (4 randomized controlled trials, 5 cohorts, and 5 case–control) studies, involving 12,904 gynecologic cancer cases, contributed to the analysis. Pooled results indicated a non-significant decrease of total gynecologic cancer risk among statin users (RR = 0.89; 95% CI, 0.78–1.01). Stratified analyses across cancer site revealed a modest protective effect of statin on ovarian cancer (RR = 0.79; 95% CI, 0.64–0.98), while no association was found for endometrial cancer (RR = 0.90; 95% CI, 0.75–1.07). The effect of statin use against cervical cancer and vulvar cancer is not conclusive. Furthermore, long-term statin use (>5 years use) did not significantly affect the risk of endometrial cancer (RR = 0.69; 95% CI, 0.44–1.10), but had an obvious decrease on the risk of ovarian cancer (RR = 0.48; 95% CI, 0.28–0.80).
Conclusions. Our results suggest that statin use was inversely associated with ovarian cancer risk, and the association was stronger for long-term statin use (>5 years). The evidence for a protective effect of statin use against other gynecologic cancers is suggestive but not conclusive, which deserves further investigation.

Contents

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Introduction

Gynecologic cancers include ovarian, endometrial (sometimes referred to as uterine cancer), vaginal, cervical, and vulvar cancer. Endometrial cancers are the most common gynecologic cancers in developed countries [1], and in 2014, 52,630 new cases will be diagnosed with an estimated 8590 deaths predicted in the USA alone [2]. Ovarian cancer is the deadliest and second most common gynecologic cancer [3], and will cause an estimated 14,270 deaths in the USA in 2014 [2]. Cervical cancer ranks behind endometrial and ovarian cancers, accounting for about 15% of all new female cancer cases in 2008 [4]. The above data highlight the importance of screening patients at highest risk and identifying chemopreventive agents for early diagnosis and timely treatment.

Statins (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors, HMG-CoA), a group of cholesterol-lowering drugs, are commonly used to treat hypercholesterolemia and prevent coronary heart disease. Preclinical studies have found that these drugs have an additional chemopreventive potential through the induction of cancer cell apoptosis [5–7] and inhibition of cancer cell growth, proliferation, invasion, and metastasis [8,9]. Furthermore, statins can affect the growth and metastasis of cancer by inhibit the synthesis of cholesterol [10], a required material for cancer growth [11]. Several epidemiologic and clinical studies have also investigated the association between statin use and gynecologic cancers [12–25]. However, the existing results are controversial, with no identified effects in the majority of studies [12–19,22,23], while others reported a reduced risk [21,25]. One study found a decreased risk in endometrial cancer but not in ovarian cancer [24], and another reported a significantly lower risk only in long-term statin use [20].

This issue has been discussed in a previously conducted meta-analysis in 2008, which suggested that statins do not have preventive effects on overall gynecologic cancer risk [26]. However, this meta-analysis focused on the risk of all cancers, and did not particularly evaluate the association between statin use and gynecologic cancers, in particular regarding sensitivity analyses, subgroup analyses, and publication bias. Given the widespread and rapidly increasing use of statins, any association with cancer risk would have a substantial public health impact. Therefore, we performed a comprehensive meta-analysis and provide a quantitative assessment of all relevant published studies to better understand the effects of statin on the risk of gynecologic cancers.

Methods

Data sources and search strategy

This study was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [27]. A systematic literature search was conducted using PubMed, Embase, and Cochrane library databases up to February 10, 2014. The search terms included "HMG-CoA reductase inhibitor(s)," "statin(s)," "atorvastatin," "cerivastatin," "fluvastatin," "lovastatin," "mevastatin," "pravastatin," "rosuvastatin," and "simvastatin" combined with "cancer," "neoplasm(s) ," and "malignancy(ies)." No language restrictions were imposed. We manually searched the bibliographies of the relevant articles, previous reviews, and meta-analysis to identify any additional studies. We also manually searched the abstracts from major gynecology and oncology conferences (2003–2014) for studies to identify unpublished results on this subject.

Eligibility criteria and study selection

Studies were included if they fully met the following criteria: (1) randomized controlled trials (RCTs), cohort studies, or case–control studies; (2) compared statin use with control (placebo or no statins); (3) reported gynecologic cancers (including cancers of the ovary, endometrium (namely uterus), cervix, vagina, or vulva) incidence; and (4) reported odds ratio (OR), relative risk (RR), or hazard ratio (HR) estimates with 95% confidence interval (CI), or provided sufficient data to reconstruct 2×2 tables for their calculation. Reviews, letters, comments, lectures, and case reports were all excluded. When there were multiple publications from the same population, only the study with larger sample size was included. Two authors (YL and AQ) independently evaluated all records by title and abstract and subsequently retrieved and assessed in detail the full text of any potentially relevant articles according to the eligibility criteria. Disagreements or uncertainties regarding eligibility were resolved through discussion with two additional adjudicators (XQ and SL).

Data extraction and quality assessment

Data were extracted from full-text articles onto a standardized form independently by two reviewers (AQ and YL). Differences were resolved by consensus, referring back to the original article. The following data were extracted: first author's name, year of publication, study location, study design, primary outcome reported, number of cases and total female subjects, study period, adjustment factors, and multivariable adjusted RR estimates with corresponding 95% CIs.

The methodological quality of RCTs was assessed using the tool of "risk of bias" according to the Cochrane Handbook; the instruments are described in detail elsewhere [28]. We used the Newcastle–Ottawa scale (NOS) to assess the quality of cohort and case–control studies [29]. In this scale, studies were awarded a maximum score of 9 points; a high-quality study was awarded ≥ 7 points, a medium-quality study between 4 and 6 points, and a poor-quality study <4 points. Two authors (YL and TL) independently assessed the methodological quality and conflicts were resolved by consensus.

Data synthesis and statistical analysis

Since cancer could be considered a relatively rare event, we assumed that ORs, risk ratios, rate ratios, and HRs were all comparable estimates of the RR [30]. Our primary analysis focused on assessing the risk of overall gynecologic cancers among statin users. When the study provided the risk estimates for site-specific cancer, we combined them to calculate a total estimate. To detect potential interactions, studies were stratified by the type of cancer (ovarian, endometrial, cervical, vaginal, and vulvar cancer). Further subgroup analysis estimated the effects of statin on gynecologic cancer risk by study design (RCT, cohort, and