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Systematic or Meta-analysis Studies

Statin use and mortality in cancer patients: Systematic review and meta-analysis of observational studies

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ABSTRACT

Background: Previous studies have examined the effect of statin use on the mortality in cancer patients, but the results are inconsistent. A meta-analysis was performed to assess the association with all available studies.

Methods: Relevant studies were identified by searching PubMed and EMBASE to April 2015. We calculated the summary hazard ratios (HRs) and 95% confidence intervals (CIs) using random-effects models. We estimated combined HRs associated with defined increments of statin use, using random-effects meta-analysis and dose–response meta-regression models.

Results: Thirty-nine cohort studies and two case-control studies involving 990,649 participants were included. The results showed that patients who used statins after diagnosis had a HR of 0.81 (95% CI: 0.72–0.91) for all-cause mortality compared to non-users. Those who used statin after diagnosis (vs. non-users) had a HR of 0.77 (95% CI: 0.66–0.88) for cancer-specific mortality. Prediagnostic exposure to statin was associated with both all-cause mortality (HR = 0.79, 95% CI: 0.74–0.85) and cancer-specific mortality (HR = 0.69, 95% CI: 0.60–0.79). Stratifying by cancer type, the three largest cancer-type subgroups were colorectal, prostate and breast cancer and all showed a benefit from statin use. HRs per 365 defined daily doses increment were 0.80 (95% CI: 0.69–0.92) for all-cause mortality and 0.77 (95% CI: 0.67–0.89) for cancer-specific mortality. A 1 year increment in duration only conferred a borderline decreased risk of death.

Conclusions: In conclusion, the average effect of statin use, both postdiagnosis and prediagnosis, is beneficial for overall survival and cancer-specific survival.

Introduction

Cancer is a very serious health problem worldwide, and is the leading cause of death in economically developed countries and the second leading cause of death in developing countries [1]. Considering the different causes, the different tissues affected, and the different symptoms, cancer is a very complex and still incurable disease. Although much effort has been directed at comprehending carcinogenesis and a lot of progress has been achieved, there is still no effective treatment for most cancers.

Recently, the potential anticancer properties of statins have attracted more interest. Statins, among the most frequently prescribed drugs worldwide, reduce serum cholesterol and prevent cardiovascular diseases [2]. They block 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which inhibits the conversion of HMG-CoA to the cholesterol precursor mevalonate, the rate limiting step in cholesterol synthesis [3]. Statins may exert their anticancer effect via lowering protein prenylation [4], reducing tumor cell proliferation and migration [5,6], inhibiting of rat sarcoma (Ras) signaling [7], inducing apoptosis through phosphorylation of Akt and down-regulation of mammalian target of rapamycin (mTOR) [8], and other pleiotropic effects on the cellular level.

In the last decade, a number of observational studies have tried to examine the effect of statin use on outcome in patients with several cancer types including breast [5,9–12], prostate [13–18], ovarian[19–21], lymphoma [22,23], renal cell carcinoma [8,24,25] and colorectal cancer [4,26–32] et al.; some have suggested that statin use was associated with longer survival, while others report no benefit. To date, no meta-analysis has been conducted concerning

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the therapeutic value of statins on the survival of cancer patients. Therefore, we performed a meta-analysis with all available studies to explore the association between pre- and post-diagnosis statin use and the survival of cancer patients, for both cancer-specific mortality and all-cause mortality. Besides, we also performed a dose–response analysis to further evaluate the potential dose–response relation.

Material and methods

Literature search

We searched PubMed (from 1981 to present) and Embase (from 1991 to present) using the following terms (''Statin'' or ''Atorvastatin'' or ''Cerivastatin'' or ''Compactin'' or ''Fluvastatin'' or ''HMG-CoA'' or ''Lovastatin'' or ''Mevastatin'' or ''Pravastatin'' or ''Rosuvastatin'' or ''Rosvastatin'' or ''Simvastatin'') and (''mortality'' or ''survival'') and ''cancer''. The latest date of this search was April 2015. All cohort or case-control studies evaluating the association between statin use and mortality in cancer patients were eligible, without language restriction. Reference lists of every article retrieved and relevant reviews were examined manually to further identify potentially relevant studies. All searches were conducted independently by two reviewers; differences were checked by the two and resolved by discussion. When two or more studies presented possible overlap, the one with largest populations was included.

Inclusion criteria

All the studies were included in this meta-analysis if they met the following criteria: (a) the exposure of interest was statin use assessed before or after diagnosis; (b) The study design was case-control or cohort; (c) the outcomes of interest were all-cause mortality or cancer-specific mortality; (d) the follow-up period was longer than 1 year; and (e) risk estimates of mortality and 95% confidence intervals (CIs) were reported (or information to calculate them).

Data extraction

Data were extracted from the eligible articles by two independent investigators. The extracted data included the last name of first author, year of publication, origin of the study, follow-up period, sample size, study design, patient characteristics, statin use, risk estimates and corresponding 95% CIs, and covariates adjusted for in the multivariable analysis. If risk estimate and corresponding 95% CI were not available [10,33,34], the data were calculated using curve method described by Tierney [35]. For studies provided more than one risk estimate, we extracted the one that was adjusted for the greatest number of confounding factors. Discrepancies were resolved by consensus, involving a third investigator.

Study quality assessment

The methodological quality of the studies included in present meta-analysis was independently assessed using the nine-star Newcastle Ottawa scale (NOS) [36] by two investigators. Each study was evaluated based on eight items, categorized into three broad perspectives including selection, comparability, and outcome for cohort studies or exposure for case-control studies. We considered studies with a score of 7 or greater as high quality. Discrepancies were resolved by discussion or through consultation with a third investigator.

Statistical methods

Because outcomes were relatively rare, the odds ratios (ORs) and relative risks (RRs) were considered approximations of hazard ratios (HRs). Summary estimates of HR and 95% CIs were obtained using a random effects model where the restricted maximum likelihood estimator was used to evaluate the inter-study heterogeneity [37,38]. Prediction interval (PI) of summary estimate for the random effects model was calculated to depict the uncertainty around the estimate [39]. If studies did not report a summary risk estimate for statin use, a summary risk estimate was calculated using risk estimates for each of the statin use categories [9]. For a study provided risk estimates for cancer-specific deaths and other-cause deaths, risk estimates for all-cause mortality were calculated firstly [14]. If studies provided separate risk estimates by statin type [11], tumor stage [9] or treatment [16] without a summary risk estimate, we treated them as different studies. Inter-study heterogeneity was estimated using a chisquare-based Q-test [40], with a P value of <0.10 considered statistically significant [41]. We also calculated the I^2 quantity [40], which lies between 0% and 100%. A value of 0% indicates no observed heterogeneity and larger values indicate increasing heterogeneity. Sensitivity analyses were performed to reflect the influence of individual data on summary HRs. Finally, the potential for publication bias was examined using Begg's and Egger's regression test [42]. Where publication bias was found, the trim-and-fill method was used to estimate the potential influence of this bias on pooled summary estimates [43].

We analyzed the association between increments in statin use and mortality in two steps. First, we used the method of Greenland and Longnecker [44] to estimate the increase in log HR per 1 unit increase of statin use. Only studies with at least three quantitative exposure levels were included in these analyses. For each study, we calculated the median level of statin use for each category by assigning the midpoint of upper and lower boundaries in each category as the average statin use level. When the highest category was open-ended [5–7,9,13,26,28,32], we assigned the lower end value of the category multiplied by 1.5. Studies were not eligible if the required data were not reported or could not be estimated. Second, the study-specific risk increments were combined in random-effects meta-analysis. All of the statistical analyses were done with R software, version 3.1.1, using the packages meta for [45] and dosresmeta [46]. All statistical tests were two-sided.

Results

Characteristics of the studies

The flow chart summarizing the process of study selection is shown in Fig. 1. Two thousand four hundred and thirty-four abstracts and titles were identified and assessed, and fifty-one studies were evaluated in detail with regard to their fulfillment of the inclusion criteria. Four articles were excluded as their outcome was not cancer-related death, or no usable data reported [47–50]. Two studies whose subjects were overlapped in another article were excluded [51,52]. Four studies were also excluded since the exposure of interest was not statin use [53–55]. Finally, thirty-nine cohort studies [4–14,16–28,30–34,56–65] and two case-control studies [15,29] involving 990,649 participants were selected for meta-analysis. Table 1 shows the characteristics of the included studies. Among these forty-one studies, twenty-nine