

Statin use and its potential therapeutic role in esophageal cancer: a systematic review and meta-analysis

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Purpose: Statins, known as inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductases, are designed to treat lipid disorders, especially hypercholesterolemia. Apart from their role in preventing heart diseases in patients with high cholesterol, recent evidence suggests that statins have anti-tumor properties. However, studies assessing the association between statin use and esophageal cancer survival outcomes have provided controversial results.

Methods: We conducted a systematic review and meta-analysis focusing on studies evaluating associations between statin use and survival outcomes for esophageal cancer patients.

Results: A total of five cohort studies comprising 24,576 patients were included. Statin use associated with improved overall survival (OS: HR 0.84, 95% CI, 0.75–0.94) and disease-free survival (DFS: HR 0.84, 95% CI, 0.75–0.96) of esophageal cancer patients. The improved survival outcomes were consistent in the esophageal adenocarcinoma subgroup and the esophageal squamous cell cancer subgroup.

Conclusion: A potential therapeutic role of statins in esophageal cancer has been demonstrated in our study, however, the results should be interpreted cautiously and need further confirmation by future studies.

Keywords: statins, esophageal cancer, survival outcome, drug repositioning

Introduction

Esophageal cancer, the sixth most common cause of cancer-related death worldwide, has become a serious public health concern.¹ It was recently estimated to account for over 16,940 new cases and 15,690 cancer-related deaths in America alone in 2017.² Although improvements in early diagnosis have marginally reduced the mortality of esophageal cancer, the prognosis of esophageal cancer patients remains unsatisfactory due to lymph node metastasis and high risk of tumor recurrence in situ after resection.³

Drug repositioning, defined as finding new indications for existing drugs, was first introduced to the public in a landmark article written by Ashburn and Thor in 2004.⁴ Drug repositioning has been proposed as a way to partly solve the gap between low productivity and ever-increasing pharmaceutical research and development spending faced by the biopharmaceutical industry.⁴ Several successful examples of drug repositioning have inspired extensive efforts to identify existing drugs with new potential unexpected benefits in diseases like cancer.⁵ A famous example of drug repositioning is thalidomide which has proven promising therapeutic effects on multiple myeloma and prostate cancer.^{6,7} Other well-known

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examples of drug repositioning include aspirin and metformin, which are reported to exert anti-cancer effects on colorectal cancer and endometrial cancer, respectively.^{8,9} Statins, known as inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductases, are designed to treat lipid disorders, especially hypercholesterolemia.¹⁰ Apart from their role in preventing heart diseases in patients with high cholesterol, recent evidence suggests that statins have anti-tumor properties.^{11,12} Preclinical studies have shown that statin use has a direct restrictive effect on the growth of human esophageal adenocarcinoma (EAC) cells.^{13,14} Additional studies demonstrated a potential preventive role of statin use on esophageal cancer.¹⁵ However, contrasting results were seen in studies assessing the association between statin use and esophageal cancer survival outcomes.

Since reviewing existing evidence can provide more comprehensive insights for further research to explore potential therapeutic effects of statins in treating esophageal cancer, we conducted a systematic meta-analysis to thoroughly investigate whether statin use exerts therapeutic effects in esophageal cancer patients.

Methods

Design

This systematic review and meta-analysis were conducted in accordance with the provisions of the Cochrane Handbook, and the results were reported following the Preferred Reporting Items of Systematic reviews and Meta-Analyses (PRISMA) guidelines.¹⁶ The 27-point PRISMA Checklist was presented in [supplementary Table 1](#).

A systematic literature search was performed of the electronic databases PubMed, Embase, and Web of Science from inception through July 22, 2018, and then updated with two additional databases (Cochrane library and clinicaltrials.gov) on March 3, 2019, without consideration of language or publication year, to include all studies investigating associations between statin use and survival outcomes for esophageal cancer patients. The databases were searched using the following strategy: (HMG-CoA reductase inhibitor* OR statin* OR atorvastatin OR fluvastatin OR lovastatin OR pravastatin OR rosuvastatin OR pitavastatin OR simvastatin) AND (cancer OR neoplasm OR tumor OR malignan*) (“*” stands for truncation searching). A manual screen of reference lists cited in the retrieved articles was also conducted to identify additional related articles.

Study selection

Studies that met the following criteria were included: 1) studies clearly enrolled patients who were adults diagnosed with esophageal cancer, 2) studies clearly defined comparison of statin use, whether to placebo or no statin use, regardless of type, dosage, or frequency, and 3) outcomes of interest were overall survival (OS), cancer-specific survival, disease-free survival (DFS), and progression-free survival (PFS). Non-original studies, such as reviews, systematic reviews and meta-analyses, case reports, editorials, and letters to editors, were excluded. When cohorts overlapped in two or more studies, only the most recent publication was included.

The title and abstract of all identified studies were independently reviewed by two reviewers (CZ and XZ) to exclude studies that clearly did not meet the inclusion criteria. The full texts of the remaining studies were further reviewed by the same two reviewers prior to final inclusion. Any discrepancies were resolved through discussions.

Data extraction

The following details were extracted from the selected studies: first author of the study, publication year, study country, study design, histological type, follow-up period, sample size, initial treatment for esophageal cancer, hazard ratios (HRs) with corresponding 95% confidence intervals (CIs), and adjustment variables. The Newcastle-Ottawa quality assessment scale (NOS) was used to evaluate the quality of eligible articles, with articles categorized as low (0–3), moderate (4–6), or high quality (7–9) according to their scores.¹⁷

Statistical analyses

Statistical analyses were conducted using STATA version 12.0 (StataCorp. LLC, College Station, TX, USA). A random-effects model was used to conduct quantitative synthesis to provide more conservative estimates,^{18,19} considering that even when the estimate of I^2 equals 0, the 95% CIs around I^2 can be wide and the upper 95% CI often exceeds the 50% threshold.²⁰ Heterogeneity among the included studies was estimated using the Cochran Q (X^2) statistic and I^2 statistic, with $I^2 > 50\%$ indicating substantial heterogeneity.²¹ Subgroup analyses were performed based on study country of origin, study design, tumor site, or treatment pattern to explore possible sources of heterogeneity. Potential publication biases were assessed using funnel plots, Begg's and Egger's tests.^{22,23} The 95% prediction interval (PI) was calculated to predict the potential effect of

statin use in an individual study setting and was more conservative than the average effect indicated by the 95% CI.²⁴

Results

Study selection and the characteristics of included studies

Of the 11,825 eligible publications in the initial database search and manual reference screening, 11,697 remained after removing duplicates. After excluding 11,579 records based on reviewing the title and abstract, 118 potentially relevant records remained for further review. A total of five cohort studies comprising 24,576 patients met the inclusion criteria after excluding 113 investigations identified as inadequate ([Supplementary Table 2](#)).^{25–29} [Figure 1](#) shows the flowchart of the study selection. All included studies were cohort studies published between 2016 and 2019 in English journals. Two were conducted in North America, two in the United Kingdom, and the remaining

one was from Belgium. Details of follow-up duration were available in Chris et al, George et al, and Lacroix et al, with median follow-up times ranging from 2 to 3.3 years.^{26,27,29} Data for OS and DFS were reported in all included studies, and these outcomes were reported both before and after adjustment in most studies. Sex, age at diagnosis, tumor grade, cancer treatment, and pre-diagnosis use of statins are frequently examined covariates adjusted for in Cox's proportional hazard model. The basic and summarized characteristics of the eligible studies are provided in [Table 1](#). The methodological quality of the included studies was deemed moderate, with all scoring six in the assessment using the NOS checklist ([Table 2](#)).

Statin use and OS

The pooled estimate of OS was 0.87(95% CI, 0.79–0.96, $I^2=78.1%$, $P_{het}<0.001$) for unadjusted HR, and 0.84 (95% CI, 0.75–0.94, $I^2=68.0%$, $P_{het}=0.005$)

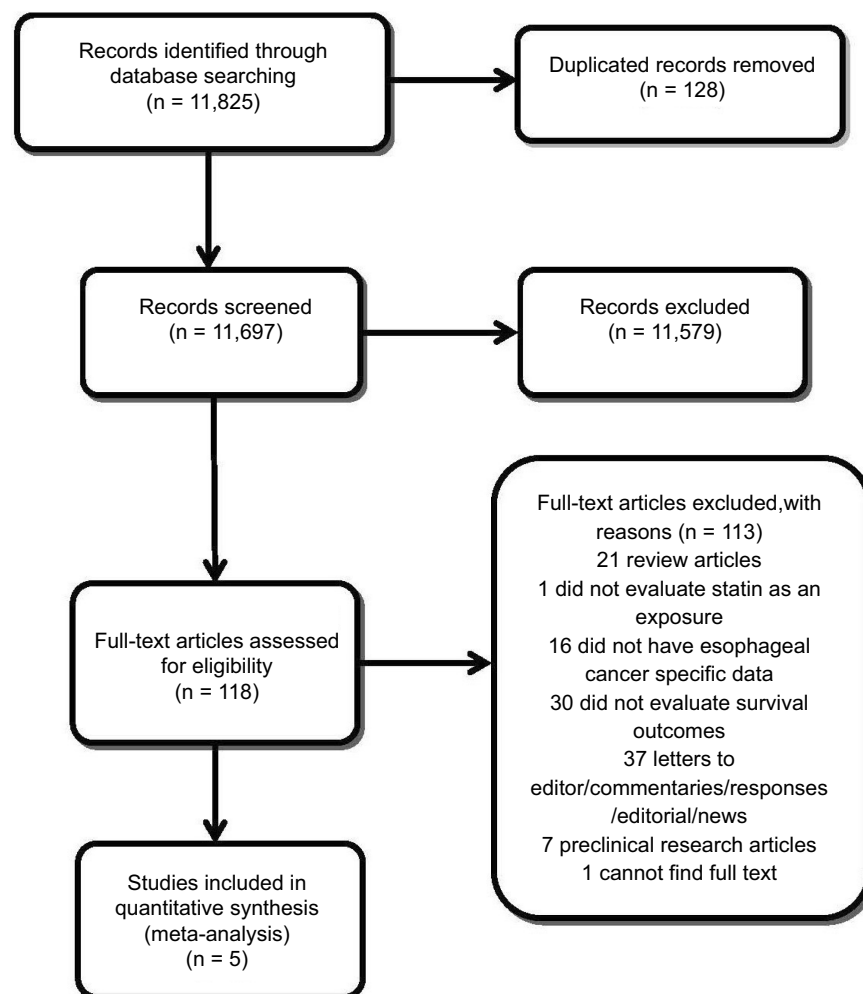


Figure 1 The selection process for the included studies.

Table 1 Baseline characteristics of included studies

Study	Publication year	Country	Study period (Follow-up period)	Study design	Population	Overall survival HR (95% CI)	Disease-free survival HR (95% CI)	Covariates in multivariable models
Chris et al. ²⁷	2017	UK	2009–2015 (median 2 years)	Retrospective Cohort	1,921	Overall: Unadjusted 1.02(0.92–1.14) Adjusted 0.94(0.82–1.07)	Overall: Unadjusted 0.97(0.86–1.09) Adjusted 0.93 (0.81–1.07) EAC: Unadjusted 0.97(0.84–1.14) Adjusted 0.90(0.75–1.08) ESCC: Unadjusted 0.99(0.80–1.21) Adjusted 0.94(0.73–1.21)	Sex, age, year of diagnosis, deprivation, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities (prior to diagnosis, including acute myocardial infarction, congestive heart disease, peripheral vascular disease, cerebral vascular accident, pulmonary disease, peptic ulcer, liver disease, diabetes, renal disease) and aspirin use (as time varying covariate)
Leo et al. ²⁸	2016	UK	2000–2011	Retrospective Cohort	4,445	Overall: Unadjusted 0.82 (0.75–0.89) Adjusted 0.67 (0.58–0.77) EAC: Unadjusted 0.75 (0.59–0.96) Adjusted 0.60 (0.43–0.92) ESCC: Unadjusted 1.12 (0.74–1.68) Adjusted 0.78 (0.41–1.50)	Overall: Unadjusted 0.71 (0.57–0.89) Adjusted: 0.62 (0.44–0.86) EAC: Unadjusted 0.70(0.51–0.96) Adjusted 0.61(0.38–0.96) ESCC: Unadjusted 1.08(0.65–1.81) Adjusted 0.65(0.29–1.46)	Age, gender, body mass index, smoking status, cardiovascular diseases, diabetes, surgery, pre-diagnosis statin use, post-diagnosis use of aspirin, beta-blockers, NSAIDs, and ACEI/ARBs, except surgery.
George et al. ²⁶	2016	USA	2003–2010 (median 3.3 years)	Retrospective Cohort	222	Adjusted 7.58(2.12–27.18)	Adjusted 6.00(1.90–18.94)	Age, BMI, AJCC stage, cancer treatment, cumulative comorbidity, presence of metastases, tumor site.

(Continued)

Table 1 (Continued).

Study	Publication year	Country	Study period (Follow-up period)	Study design	Population	Overall survival HR (95% CI)	Disease-free survival HR (95% CI)	Covariates in multivariable models
Theresa et al. ²⁵	2018	USA	2002–2016	Retrospective Cohort	11,750	EAC: Unadjusted 0.82(0.77–0.87) Adjusted 0.80 (0.74–0.86) ESCC: Unadjusted 0.76(0.68–0.84) Adjusted 0.83(0.74–0.95)	EAC: Unadjusted 0.79(0.72–0.87) Adjusted 0.79(0.70–0.88) ESCC: Unadjusted 0.71 (0.60–0.83) Adjusted 0.77(0.63–0.92)	Age, sex, race, BMI, alcohol use, smoking status, stage, grade, treatment (surgery, chemotherapy, radiation), post-diagnosis uses of aspirin or NSAIDs (time-varying), and pre-diagnosis use of statins.
Lacroix et al. ²⁹	2019	Belgium	2004–2016 (median 2.39 years)	Retrospective Cohort	6,238	Unadjusted 0.92(0.85–1.00) Adjusted 0.84(0.77–0.92)	Unadjusted 0.88(0.80–0.98) Adjusted 0.87(0.78–0.97)	Age, sex, year of diagnosis, comorbidities, cancer treatment within 6 months after diagnosis, and cancer histology.

Abbreviations: UK, United Kingdom; USA, United States of America; HR, hazard ratio; CI, confidence interval; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma.

Table 2 The NOS quality of included studies

Study	Selection				Comparability		Outcome			Total	Quality
	REC	SNEC	AE	DO	SC	AF	AO	FU	AFU		
Chris et al. ²⁷		0			0	0				6	Moderate
Leo et al. ²⁸		0			0	0				6	Moderate
George et al. ²⁶		0			0	0				6	Moderate
Theresa et al. ²⁵		0			0	0				6	Moderate
Lacroix et al. ²⁹		0			0	0				6	Moderate

Note: “|” means that the study satisfied the item and “0” means the opposite situation.

Abbreviations: REC, representativeness of the exposed cohort; SNEC, selection of the nonexposed cohort; AE, ascertainment of exposure; DO, demonstration that outcome of interest was not present at start of study; SC, study controls for age, sex; AF, study controls for any additional factors; AO, assessment of outcome; FU, follow-up long enough (36M) for outcomes to occur; AFU, adequacy of follow-up of cohorts ($\geq 90\%$).

for adjusted HR (Figure 2A and B). No evidence of publication bias was found via funnel plot, Begg’s test ($P=0.71$ for unadjusted HR, $P=0.55$ for adjusted HR), or Egger’s test ($P=0.73$ for unadjusted HR, $P=0.41$ for adjusted HR). We performed a subgroup analysis based on the two main histological subtypes of esophageal cancer. In the EAC subgroup, the pooled estimate of OS was 0.82 (95% CI 0.77–0.87, $I^2=0.0\%$, $P_{\text{het}}=0.486$) for unadjusted HR, and 0.74 (95% CI 0.57–0.95, $I^2=52.7\%$, $P_{\text{het}}=0.146$) for adjusted HR. In the esophageal squamous cell cancer (ESCC) subgroup, the pooled estimate of OS was 0.88 (95% CI 0.61–1.26, $I^2=69.0\%$, $P_{\text{het}}=0.073$) for unadjusted HR, and 0.83 (95% CI 0.73–0.94, $I^2=0.0\%$, $P_{\text{het}}=0.854$) for adjusted HR.

Statin use and DFS

The pooled estimate of DFS was 0.84 (95% CI, 0.77–0.92, $I^2=55.9\%$, $P_{\text{het}}=0.034$) for unadjusted HR, and 0.84 (95% CI 0.75–0.96, $I^2=59\%$, $P_{\text{het}}=0.017$) for adjusted HR (Figure 2C and D). No evidence of publication bias was found via funnel plot, Begg’s test ($P=1.00$ for unadjusted HR, $P=0.71$ for adjusted HR), or Egger’s test ($P=0.65$ for unadjusted HR, $P=0.47$ for adjusted HR). The subgroup analysis showed that the pooled estimate of DFS was 0.83 (95% CI 0.70–0.99, $I^2=67.5\%$, $P_{\text{het}}=0.046$) for unadjusted HR, and 0.81 (95% CI 0.71–0.93, $I^2=31.2\%$, $P_{\text{het}}=0.234$) for adjusted HR in the EAC subgroup, and 0.87 (95% CI 0.66–1.15, $I^2=72.7\%$, $P_{\text{het}}=0.026$) for unadjusted HR, 0.82 (95% CI 0.71–0.95, $I^2=0.0\%$, $P_{\text{het}}=0.394$) for adjusted HR in the ESCC subgroup.

Due to insufficient data provided in the included studies, we were unable to investigate associations between

statin use and risks of progression, recurrence, or metastasis.

Discussion

Main findings and interpretation in light of the evidence

Statins are commonly prescribed cholesterol-lowering agents with an established human safety profile. Statins were recently reported to have anti-cancer activity, making them good candidates for drug repositioning. A series of basic studies have shown that statins inhibit the proliferation of EAC and ESCC cell lines by promoting apoptosis.^{14,30} A recent systematic review and meta-analysis also reported that statins may play a preventive role against developing esophageal cancer in subjects with or without Barrett’s esophagus.³¹ Results from epidemiologic studies have demonstrated that statin use after diagnosis is associated with reduced mortality from a range of malignant tumors, including breast, colorectal, and prostate carcinomas.^{32,33} However, controversies remain between studies exploring whether statin use improves the survival outcomes of esophageal cancer patients.

In this meta-analysis, we systematically and comprehensively assessed all studies that we could access that investigated the associations between statin use and survival outcomes for esophageal cancer patients. Among the five included studies comprising 24,576 esophageal cancer patients, we found that statin use statistically significantly reduced both all-cause mortality and cancer-specific mortality by 16%. It is worth addressing that we chose a random-effects model to provide more conservative results than a fixed-effects model could, accounting for the significant heterogeneity shown in our quantitative

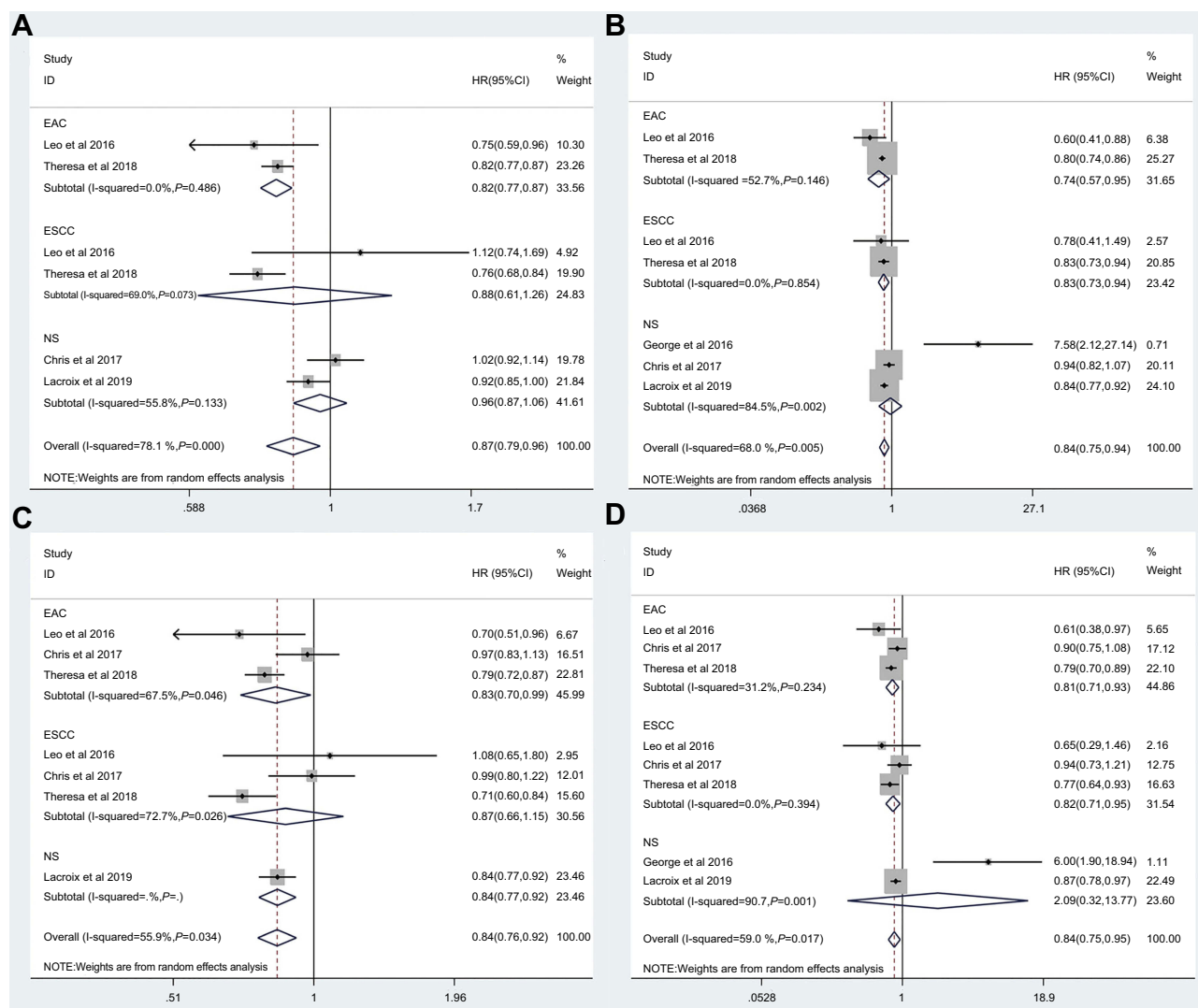


Figure 2 (A) The pooled estimate of unadjusted OS. (B) The pooled estimate of adjusted OS. (C) The pooled estimate of unadjusted DFS. (D) The pooled estimate of adjusted DFS.

Abbreviations: EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; NS, not specified.

syntheses. Furthermore, we performed subgroup analyses based on histological subtypes to explore the origin of the observed heterogeneity. The statistically significant heterogeneity no longer persisted in EAC and ESCC subgroups in the meta-analyses of adjusted or unadjusted HR for OS and adjusted HR for DFS, but it persisted in the meta-analysis of unadjusted HR for DFS, suggesting that histological subtype may partially account for the observed heterogeneity. Meanwhile, subgroup analysis demonstrated a 19% reduced risk in DFS rates and 26% reduced risk in OS rates in the EAC subgroup, with 18% and 17% reductions, respectively, in the ESCC subgroup. All results of overall synthesis and subgroup analysis reached statistical significance, indicating that statins improve OS and

DFS in esophageal cancer patients irrespective of histological subtype. The funnel plots, Begg's test, and Egger's test showed no indication of publication bias, strengthening the validity of this work. It is worth mentioning that George et al,²⁶ which only provided adjusted HRs for OS and DFS, had a sample size (222) much smaller than the other four studies (1,921, 4,445, 11,750, and 6,238), and caused substantial variance considering the broad 95% CI. When we re-performed the quantitative syntheses of adjusted HR and 95% CI excluding George et al, the overall effect of statin uses on improving OS (adjusted HR:0.83, 95% CI 0.78–0.89, $P<0.001$) and DFS (adjusted HR:0.83, 95% CI 0.78–0.89, $P<0.001$) was even more significant, suggesting that potential therapeutic effects of

statins for esophageal cancer patients may be confirmed by acquiring sufficient data and decreasing heterogeneity. Our results indicate a potential overall therapeutic effect of statins on esophageal cancer, regardless of histological subtype. To better probe this therapeutic role of statins in clinical practice, we calculated the 95% PI to explore the therapeutic effects on an individual study level. The 95% PI for OS (0.46–1.45) and DFS (0.43–1.51) both crossed the value of one, possibly because we only included five studies of relatively small sample sizes and with substantial heterogeneity. Thus, the results of our study require further confirmation with more large-scale studies and should currently be interpreted with caution. Nonetheless, this study demonstrates a potential therapeutic effect of statins and a promising future for further recommendation of statins as an alternative option for current treatment strategies.

Strengths and limitations

This is the first meta-analysis to address the association between statin use and survival outcomes of esophageal cancer patients. Furthermore, we calculated the 95% PI in our study which has rarely been included in previous meta-analyses studying the association between statin use and survival outcomes in other cancers.²⁴ In contrast to CI, PI predicts the potential therapeutic effect of statin use on esophageal cancer patients in an individual study setting and is more applicable to translating meta-analysis results into clinical practice.²⁴

Still, our study has several limitations. First, the number of included studies is limited, so the statistically-significant results found here need further confirmation by relevant future studies. Second, due to insufficient data provided in the included studies, we focused mainly on two survival outcomes, OS and DFS, and were unable to investigate associations between statin use and risk of progression, recurrence or metastasis, which are all critical indicators of the prognosis of esophageal cancer patients. Third, substantial heterogeneity exists among the included studies due to the divergent type, dose, duration, and pattern of statin use and the innate differences of research centers and populations. These limitations are largely caused by the insufficient data available. Our team will update this systematic review and meta-analysis when more data are provided in future studies.

Conclusion

In conclusion, this study demonstrates that statins may improve OS and DFS in esophageal cancer patients. However, the potential therapeutic roles of statins in esophageal cancer should be interpreted cautiously and need further confirmation by future studies.

Abbreviation list

HMG CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; RCT, randomized controlled trials; OS, overall survival; RFS, recurrence-free survival; CSS, cancer-specific survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; PI, prediction interval; PRISMA, The Preferred Reporting Items of Systematic reviews and Meta-Analyses; NOS, the Newcastle-Ottawa quality assessment scale.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years and no other relationships or activities that could appear to have influenced the submitted work. The authors report no conflicts of interest in this work.

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