Meta-Analysis of Observational Studies in Epidemiology

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Impact of statin use on cancer-specific mortality and recurrence

A meta-analysis of 60 observational studies

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Abstract

This meta-analysis mainly summarized the studies reporting an association between statin use and cancer-specific mortality and recurrence or progression of cancer patients.

We systematically searched for studies about the statin used in cancer patients in electronic databases, including PubMed, Web of Science, Cochrane, Clinical Trials, from inception through the November 2019. A total of 60 studies which included 953,177 participants were eligible with 233,322 cancer patients used statin. Our analysis selected studies presented with outcome based on hazard ratios (HRs) and 95% confidence intervals (CIs) of cancer-specific mortality and cancer recurrence-free survival or progression-free survival. Heterogeneity between the studies was examined using I^2 statistics, and sensitivity analyses were conducted to assess the robustness of the findings. All statistical analyses were performed using RevMan software (version 5.3).

The use of statin was potentially associated with a decline in cancer-specific mortality in cancer patients (HR = 0.78; 95% CI: 0.74, 0.84; n = 39; I^2 = 85%). Furthermore, statin use was associated with improved recurrence-free survival (HR = 0.87; 95% CI: 0.78,0.97; n = 23; I^2 = 64%), but not with improvement in progression-free survival (HR = 1.05; 95% CI: 0.95,1.16; n = 14; I2 = 38%).

The meta-analysis demonstrated that statin use could exhibit potential survival benefit in the prognosis of cancer patients. But our results are conservative for statins to improve disease recurrence and progression. These findings should be assessed in a prospective randomized cohort.

Abbreviations: CIs = confidence intervals, HRs = hazard ratios.

Keywords: cancer specific mortality, HMG-CoA inhibitors, recurrence, statin

1. Introduction

Statins are inhibitors of the 3-hydroxy-3-methylglutaryl-CoA reductase, the rate-limiting enzyme of this pathway, are often used as a lipid-lowering drug to reduce cholesterol levels, as well as preventing heart disease and stroke.[1] Statin therapy is recommended for the treatment of hyperlipidemia as well as the primary and secondary prevention of cardiovascular diseases, include ischemic coronary artery disease and heart failure.[2] Cancer is not 1 condition but a variety of diseases caused by different cellular derangements. It is well known that statins were related to suppressing tumor growth and metastases and inducing

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The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved. All analyses were based on previous published studies; thus, no ethical approval and patient consent were required.

The authors have no conflicts of interest to disclose.

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apoptosis.[3–5] At the same time, some studies have found statin may induce metabolic modulation in tumors through inhibition of monocarboxylate transporters function.[6] These seem to support the beneficial effect and the mechanism of statin use on cancer patients. Based on these findings, several studies demonstrated that persistent use of statins was associated with a lower cancer risk.[7,8] However, we also found some studies shown that statins may increase the risk of cancer.[9,10]

We focused primarily on cancer-related mortality among studies, and secondly collected the literatures on recurrence or progression. Cohort studies[11,12] suggested the use of statins improved cancer overall survival. However, other cohort studies did not suggest the beneficial effects of statin use on prognosis.[13,14] In addition, there were meta-analyses that clarified the relationship between all-cause mortality or survival rates in cancer patients and statin use.[15–17] Similarly, with regards to the recurrence of cancer, use of statins was suggestive of a decreased risk of recurrence.[18,19] However, according to their results, the current opinion, on the prognostic role of statin in cancer is still controversial. Finally, we carried out a meta-analysis to assess whether statins were associated with cancer-specific mortality and cancer recurrence or progression.

2. Materials and methods

2.1. Search strategy and study selection

An electronic search of PubMed, Web of Science, Cochrane, Clinical Trials databases for all about statin and cancer prognosis studies was selected. The last search was updated in November 2019. Application search engines was chrome. Key words were carried out using the following search terms: "Hydroxymethylglutaryl-CoA Reductase Inhibitors, HMG-CoA Reductase Inhibitors or statin " and "cancer, carcinoma, tumor or neoplasms" and "recurrence, mortality and prognosis or outcome ". The search was limited to English language articles.

The search was conducted by 2 authors (Yang and Shen). We read titles and abstracts of all candidate articles. Articles were independently read and checked for inclusion criteria of articles in this study. Any disagreements were resolved through consensus with a third investigator (Zhou).

2.2. Selection criteria

All studies investigating the association between statin use and cancer-specific mortality or recurrence were considered relevant to this meta-analysis. Studies were eligible if all the following inclusion criteria were fulfilled:

(1) The study was an original observational study,
(2) the study evaluated the association between statin use and cancer-specific mortality, recurrence or progression,
(3) The results estimated hazard ratio (HR)with corresponding 95% confidence intervals (95% Cls),
(4) published as a full paper in English.

However, studies were not included if they were reviews, letters, or case reports. If duplicated samples of population were identified in different studies, the largest 1 was included.

2.3. Data extraction and study quality assessment

The following data was collected by two reviewers independently: name of first author, publishing time, study design, number of participants, cancer sites, period of follow-up, country/database, adjusted variables, the HR estimates and its 95% Cis. The main findings reported in each study were organized into 1 table.

As only observational studies were included in our study selection process, Newcastle–Ottawa scale [20] which was recommended for case-control and cohort studies by the Cochrane Collaboration was used to assess the risk of bias. We chose studies which a minimum score was 7 representing the lowest risk of bias.

2.4. Statistical analyses

The results of interest were based on cancer-specific mortality using statins before or after cancer diagnosis. The inverse variance method was used to pool the hazard ratios (HRs) for effect of statin on outcomes in cancer patients. If studies reported risk estimate at cancer-specific mortality(CSM) and all-cause mortality, the risk estimates for CSM were calculated first. If there were estimates for CSM based on statin use before cancer diagnosis, we considered the estimates as a subgroup of mortality studies. We also carried out the subgroup analysis by cancer types. The I^2 statistic was used to assess the heterogeneity across studies. If significant or substantial heterogeneity was found ($I^2 > 50\%$), the random-effect model was considered more appropriate for statistical analysis. If not, a fixed model would be preferred. All statistical analyses were performed with RevMan software (version 5.3). The potential publication bias was assessed by funnel plot visual inspection for all comparisons.

2.5. Subgroup analysis and sensitivity analysis

In all the 60 studies, we found ten articles with data on the relationship between pre-diagnostic statin use and cancer-related mortality. Meanwhile, subgroup analysis and sensitivity analysis were performed according to tumor location, follow-up time, complications and drug combination.

3. Results

3.1. Study characteristics and publication bias

By the initial search, including PubMed, Science of Science identified 2,642 potentially relevant articles. We also searched the Cochrane Library and Clinical Trials, which were 16, 8 eligible studies, respectively. Then, 519 articles were excluded due to repetition. After carefully reading the subject and abstract of the article, 1756 articles were excluded due to the apparent lack of relevance. Then exclude review, letters, non-English studies and meta-analysis, with a total of 178 full-text articles. Finally, we exclude articles that are inconsistent with the results indicators we are studying. This meta-analysis includes 60 articles (Fig. 1).[14,16,21–78] One of the articles[70] was divided into 2 sets of data by Lipophilic statin and hydrophilic statin. Authors identified 60 potential studies for full-text review, with excellent agreement between authors. The main features of eligible studies are summarized in Table 1.

There were 56 cohort studies and 4 case–control studies included in the meta-analysis.[16,23,36,64] There was nine prospective cohort in all cohort studies, and 47 retrospective cohort. Of the 60 studies, 38 investigated the association of statin use with cancer-specific mortality and 23 investigated the association of cancer recurrence, and 13 looked at cancer

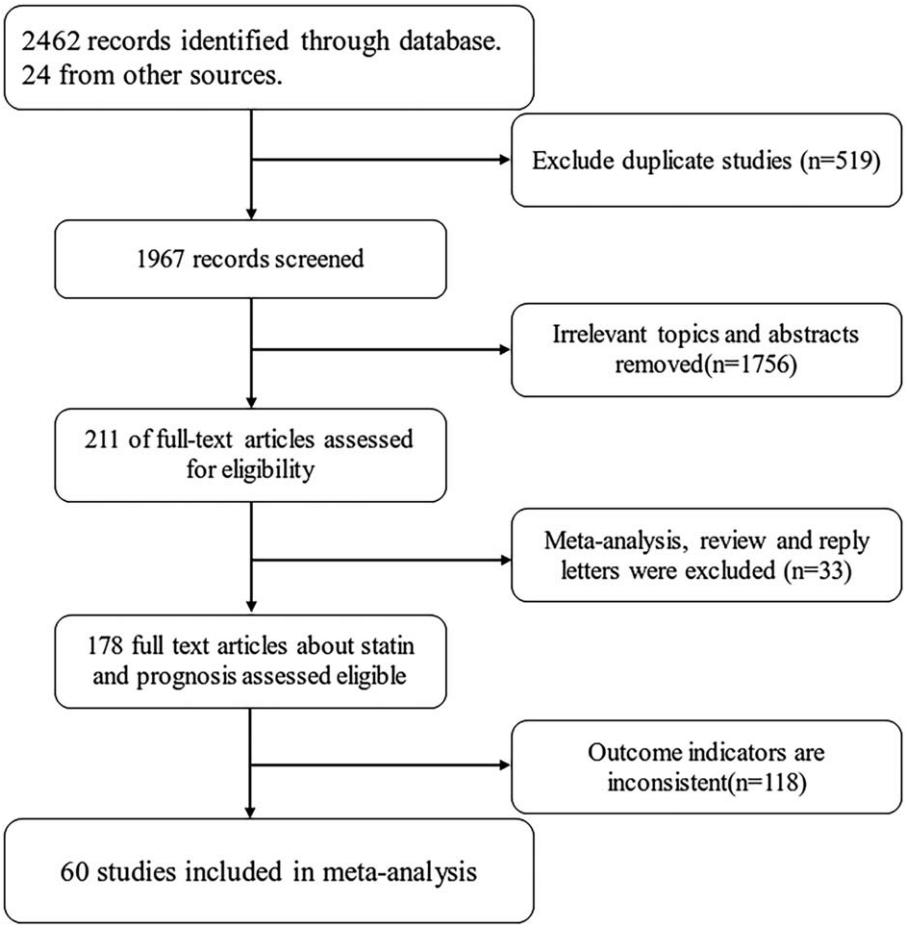

Figure 1. Flow chart representing the selection process.

progression-free survival. The total statin use cases were 233,322, most from western country. Eight studies [16,23,32,37,38,43,48,65] lacked follow-up period or did not describe the specific time of follow-up.

The shape of funnel plot showed asymmetry of included studies. Potential publication bias was revealed through it (Fig. 2).

3.2. Cancer-specific mortality

The main result of the present meta-analysis was as follows: A meta-analysis of 38 studies, include 39 data showed a reduction in cancer-specific mortality in statin users (HR = 0.78; 95% CI: 0.74, 0.84; I2 = 85%). (Fig. 3). Subgroup analysis according to the treatment strategy was performed. Eleven studies [22,25,26,28,33, 40,41,47,50,62,63] investigated the association between pre-diagnostic statin use and CSM, the summarized HR was 0.81 (95%CI = 0.75,0.88). Seven studies about breast cancer-specific mortality draw a conclusion was HR (0.79;95% CI: 0.63– 0.99), there were 7 colorectal cancer studies about Smythe pooled HR was 0.76 (95% CI:0.67–0.86). And then subgroup of prostate cancer-specific mortality outcome was HR (0.72;95% CI: 0.61 – 0.85).

3.3. Cancer recurrence

In total, 23 studies were included in the analysis of cancer recurrence. Statin use was associated with reduced cancer recurrence (HR = 0.87; 95% CI: 0.78,0.97; n = 23; $I^2 = 64\%$) (Fig. 4). In subgroup analysis, for 9 studies investigated the association between statin use and prostate cancer recurrence, the summarized HR was 0.89 (95%CI = 0.74,1.07). Perhaps the use of statins could not improve cancer-specific recurrence in prostate cancer.

3.4. Progression-free survival

In this meta-analysis, there are 13 articles containing the outcome index for progression-free survival. Since an article examined hydrophilic statins and lipophilic statins, 14 sets of data were included. We draw a conclusion in this analysis that statin use was not associated with reduced cancer progression-free survival (HR = 1.05; 95% CI: 0.95,1.16; n = 14; $I^2 = 38\%$). (Fig. 5)

3.5. Sensitivity analyses of CSM and recurrence

Due to the high heterogeneity of this research, we performed 5 sensitivity analyses. In the first sensitivity analysis of CSM, 10 studies with median 5 years or longer follow-up duration were included, (pooled HR, 0.80; 95% CI: 0.73 to 0.87). In the second sensitivity analysis of CSM, 20 studies that provided adjustments to concomitant drug were included (pooled HR, 0.82; 95% CI: 0.77 to 0.87). The concomitant drug included aspirin, other nonsteroidal anti-inflammatory drugs, angiotensin converting

Table 1

Characteristics of included studies.

Characteristics	Number of studies (%)	Total sample size (%)	Statin user (%)	Reference
Total	60	953177	233322	
Year of publication, No. (%)				
before2011	7 (11.7)	26261 (2.8)	4695 (2.0)	72–78
2012-2014	13 (21.7)	343316 (36.0)	28425 (12.2)	16, 60 – 71
2015-2017	23 (38.3)	142057 (14.9)	38615 (16.6)	14, 38 – 59
2018-2019	17 (28.3)	441543 (46.3)	161587 (69.2)	21-37
Study design, No. (%)				
Prospective	9 (15.0)	61173 (6.4)	9506 (4.1)	32, 38, 46, 51, 62, 67, 70, 72, 75
Retrospective	47 (78.3)	889262 (93.3)	222518 (95.5)	21, 22, 24–31, 33–35, 37, 14, 39, 41–50, 52–61, 63, 65, 66, 68, 69, 71, 73, 74, 76-78
case/control	4 (6.7)	2742 (0.3)	1298 (0.6)	16, 23, 36, 64
Cancer site, No. (%)				
all	1 (1.7)	295925 (31.0)	18721 (8.0)	71
bladder	2 (3.3)	2619 (0.3)	983 (0.4)	66, 68
breast	9 (15)	110776 (11.6)	29285 (12.5)	22, 31, 45, 46, 56, 62, 70, 74, 75
colorectal	9 (15)	52100 (5.5)	12928 (5.5)	16, 23, 29, 38, 48, 51, 59, 63, 72
endometrial	2 (3.3)	7679 (0.8)	1207 (0.5)	33, 52
esophageal	3 (5)	19909 (2.1)	5100 (2.2)	26, 37, 40
gastric	1 (1.7)	241 (0.0)	65 (0.0)	64
hepatocellular	1 (1.7)	15422 (1.6)	2293 (1.0)	25
head and neck	1 (1.7)	1194 (0.1)	572 (0.3)	36
lung	2 (3.3)	4632 (0.5)	2192 (0.9)	35, 50
ovarian	4 (6.6)	12472 (1.3)	2288 (1.0)	14, 30, 42, 65
pancreatic	4 (6.6)	1374 (0.1)	305 (0.1)	32, 43, 44, 58
prostate	18 (30)	424711 (44.6)	156141 (66.9)	21, 24, 27, 28, 34, 39, 41, 47, 49, 54, 60, 61, 67, 69, 73, 76-78
renal	3 (5)	4123 (0.4)	1242 (0.5)	53, 55, 57
Follow up period, No. (%)				
more than 5 yr	20 (33.3)	366488 (38.5)	113311 (48.6)	21, 22, 28, 31, 35, 41, 47, 53, 56, 60, 61, 63, 66, 67, 69, 70, 72-75
less than 5 yr	32 (53.3)	550321 (57.7)	109462 (46.9)	14, 24–27, 29, 30, 33, 34, 36, 39, 40, 42, 44, 45, 46, 49–52, 54, 55, 57–59, 62, 64, 68, 71, 76-78
not say	8 (13.3)	36368 (3.8)	10549 (4.5)	16, 23, 32, 37, 38, 43, 48, 65
Location, No. (%)				
Asian	5 (8.3)	26175 (2.8)	4920 (2.1)	27, 35, 43, 54, 59
America	30 (50.0)	406608 (42.6)	146196 (62.7)	21, 24, 25, 30–32, 34, 36, 37, 44, 52, 53, 55, 57, 58, 60, 61, 64–70, 72–74, 76-78
Europe	25 (41.7)	520394 (54.6)	82206 (35.2)	14, 16, 22, 23, 26, 28, 29, 33, 38–42, 45–50, 51, 56, 62, 63, 71, 75
NOS score, No. (%)				
<8	35 (58.3)	394260 (41.4)	119950 (51.4)	14, 16, 21–23, 26–29, 31, 32, 35–37, 43, 44, 46–49, 52–55, 57, 59, 60, 64–66, 68, 70, 74, 76, 78
>=8	25 (41.7)	558917 (58.6)	113372 (48.6)	24, 25, 30, 33, 34, 38–42, 45, 50, 51, 56, 58, 61–63, 67, 69, 71–73, 75, 77
Adjusted for comorbidity, No. (%)				
No	39 (65)	544920 (57.2)	107702 (46.2)	16, 23–25, 27, 31, 32, 34, 35, 38, 41, 43, 44, 47–49, 53–62, 64–68, 70–73, 75-78
Yes	21 (35)	408257 (42.8)	125620 (53.8)	14, 21, 22, 26, 28–30, 33, 36, 37, 39, 40, 42, 45, 46, 50–52, 63, 69, 74
Studies adjusted for drug, No. (%)				
No	37 (61.4)	549806 (57.7)	116520 (50.0)	14, 22–24, 28–32, 34–37, 43, 48, 49, 52–62, 64, 66, 68–71, 74, 76-78
Yes	23 (38.3)	403371 (42.3)	116802 (50.0)	16, 21, 25–27, 33, 38–42, 44–47, 50, 51, 63, 65, 67, 72, 73, 75
Outcome indicate, No. (%)				
CSM	38 (63.3)	915447 (96.0)	225176 (96.5)	14, 16, 21, 22, 24–30, 33, 36–42, 45–48, 50–53, 56, 57, 59, 62, 63, 65–68, 70, 71
RFS	23 (38.3)	63916 (6.7)	16354 (7.0)	23, 31, 35, 44, 47, 48, 51, 54, 55, 58, 60, 61, 64, 66, 67, 68, 69, 72, 73, 74, 75, 76, 77
PFS	13 (21.7)	10556 (1.1)	2790 (1.2)	23, 29, 32, 34, 43, 49, 53, 65, 66, 69, 70, 72, 78

PFS = progression-free survival, RFS = recurrence-free survival.

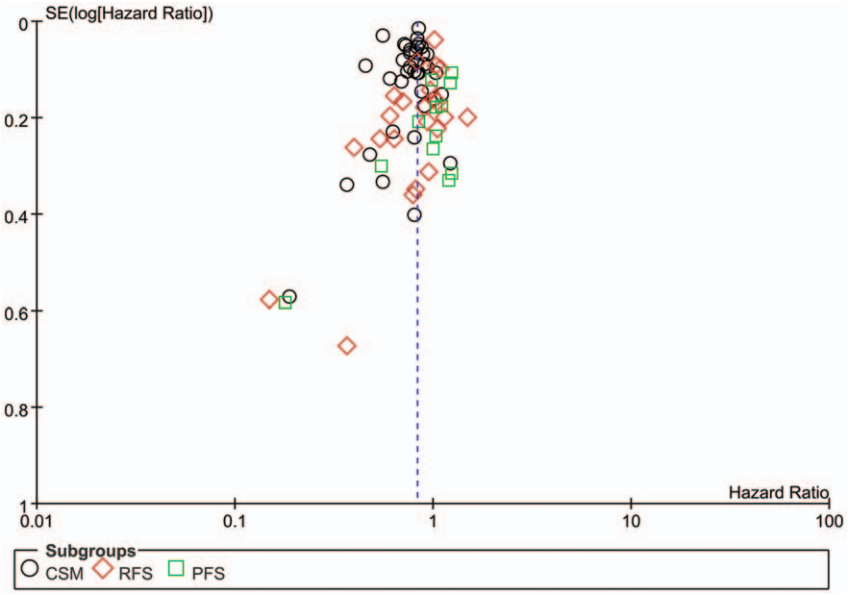

Figure 2. Funnel plot of studies in meta-analysis.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Fatim Lakha2012	-0.57982	0.333044	0.8%	0.56 [0.29, 1.08]	2012
Sune F. Nielsen2012	-0.16252	0.015099	4.1%	0.85 [0.83, 0.88]	2012
Geybels, M.S.2013	-1.66073	0.569794	0.3%	0.19 [0.06, 0.58]	2013
Brewer, T.M.2013（L）	0.16551444	0.39598967	0.6%	1.18 [0.54, 2.56]	2013
Crivelli, J.J.2013	0.207014	0.294634	0.9%	1.23 [0.69, 2.19]	2013
Da Silva, R.D.2013	0.039221	0.107452	2.8%	1.04 [0.84, 1.28]	2013
Brewer, T.M.2013（H）	-0.16251893	0.31316439	0.8%	0.85 [0.46, 1.57]	2013
Cardwell, C.R. 2014	-0.34249	0.081618	3.3%	0.71 [0.61, 0.83]	2014
Mohammed Habis2014	-0.22314	0.241783	1.2%	0.80 [0.50, 1.28]	2014
Murtola,T.J.2014	-0.77653	0.094323	3.1%	0.46 [0.38, 0.55]	2014
Viers, B.R.2015	0.019803	0.160819	2.0%	1.02 [0.74, 1.40]	2015
Cardwell, C.R.breast2015	-0.17435	0.108389	2.8%	0.84 [0.68, 1.04]	2015
Kaffenberger, S.D.2015	-0.73397	0.277203	1.0%	0.48 [0.28, 0.83]	2015
Cardwell, C.R.lung2015	-0.11653	0.068435	3.5%	0.89 [0.78, 1.02]	2015
Shao, Y.2015	-0.26136	0.065773	3.6%	0.77 [0.68, 0.88]	2015
Hoffmeister, M.2015	0.10436	0.15406	2.1%	1.11 [0.82, 1.50]	2015
Nicole S.2015	-0.46204	0.231184	1.3%	0.63 [0.40, 0.99]	2015
Mc Menamin, Ú.C.2016	-0.07257	0.095585	3.0%	0.93 [0.77, 1.12]	2016
Timothy L. Lash2016	-0.3285	0.04976	3.8%	0.72 [0.65, 0.79]	2016
Keskiväli, T.2016	-0.21072	0.400731	0.6%	0.81 [0.37, 1.78]	2016
Smith, A.2016	-0.12783	0.146051	2.2%	0.88 [0.66, 1.17]	2016
Larsen, S.B.2017	-0.18633	0.036947	4.0%	0.83 [0.77, 0.89]	2017
Couttenier, A.2017	-0.19845094	0.06528913	3.6%	0.82 [0.72, 0.93]	2017
Verdoodt, F.2017	-0.10536	0.089642	3.1%	0.90 [0.75, 1.07]	2017
Murtola,T.J.2017	-0.22314	0.10474	2.9%	0.80 [0.65, 0.98]	2017
Gray, R.T.2017	-0.09431	0.176823	1.8%	0.91 [0.64, 1.29]	2017
Cardwell, C.R.2017	-0.07257	0.071015	3.5%	0.93 [0.81, 1.07]	2017
Nguyen, T.2018	-0.26136	0.096595	3.0%	0.77 [0.64, 0.93]	2018
Lebo, N.L.2018	-0.37106	0.127462	2.5%	0.69 [0.54, 0.89]	2018
Dyg Sperling, C.2018	-0.4943	0.120562	2.6%	0.61 [0.48, 0.77]	2018
Borgquist, S.2019	-0.18633	0.054875	3.7%	0.83 [0.75, 0.92]	2019
Lacroix, O.2019	-0.13926	0.055613	3.7%	0.87 [0.78, 0.97]	2019
Kotti, A.2019	-0.99425	0.339854	0.7%	0.37 [0.19, 0.72]	2019
Harding, B.N.2019	-0.30111	0.106254	2.9%	0.74 [0.60, 0.91]	2019
Joentausta, R.M.2019	-0.18633	0.109703	2.8%	0.83 [0.67, 1.03]	2019
Van Rompay, M.I.2019	-0.31471	0.052243	3.8%	0.73 [0.66, 0.81]	2019
Thrift, A.P.2019	-0.16252	0.048162	3.8%	0.85 [0.77, 0.93]	2019
Wu, S.2019	-0.27444	0.059908	3.6%	0.76 [0.68, 0.85]	2019
Anderson-Carter, I.2019	-0.57982	0.031646	4.0%	0.56 [0.53, 0.60]	2019
Total (95% CI)			**100.0%**	**0.78 [0.74, 0.84]**	

Heterogeneity: Tau² = 0.02; Chi² = 245.67, df = 38 (P < 0.00001); I² = 85%
Test for overall effect: Z = 7.58 (P < 0.00001)

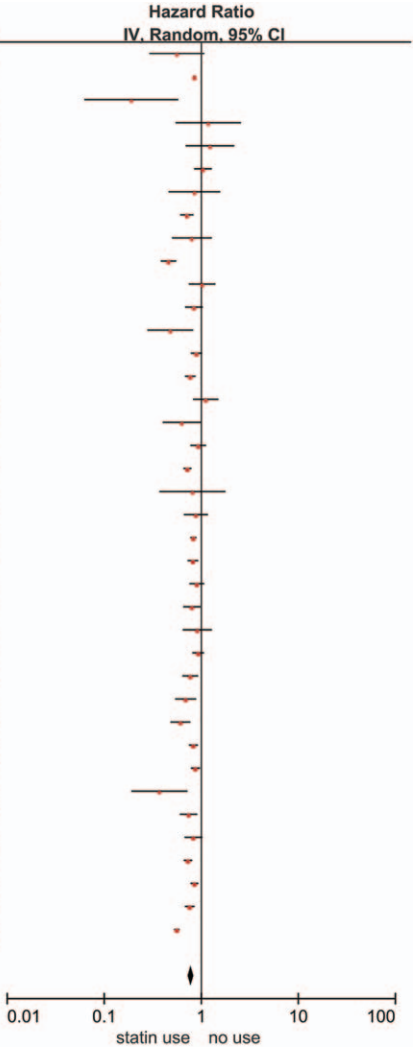

Figure 3. Forest plot of statin use and cancer-specific mortality.

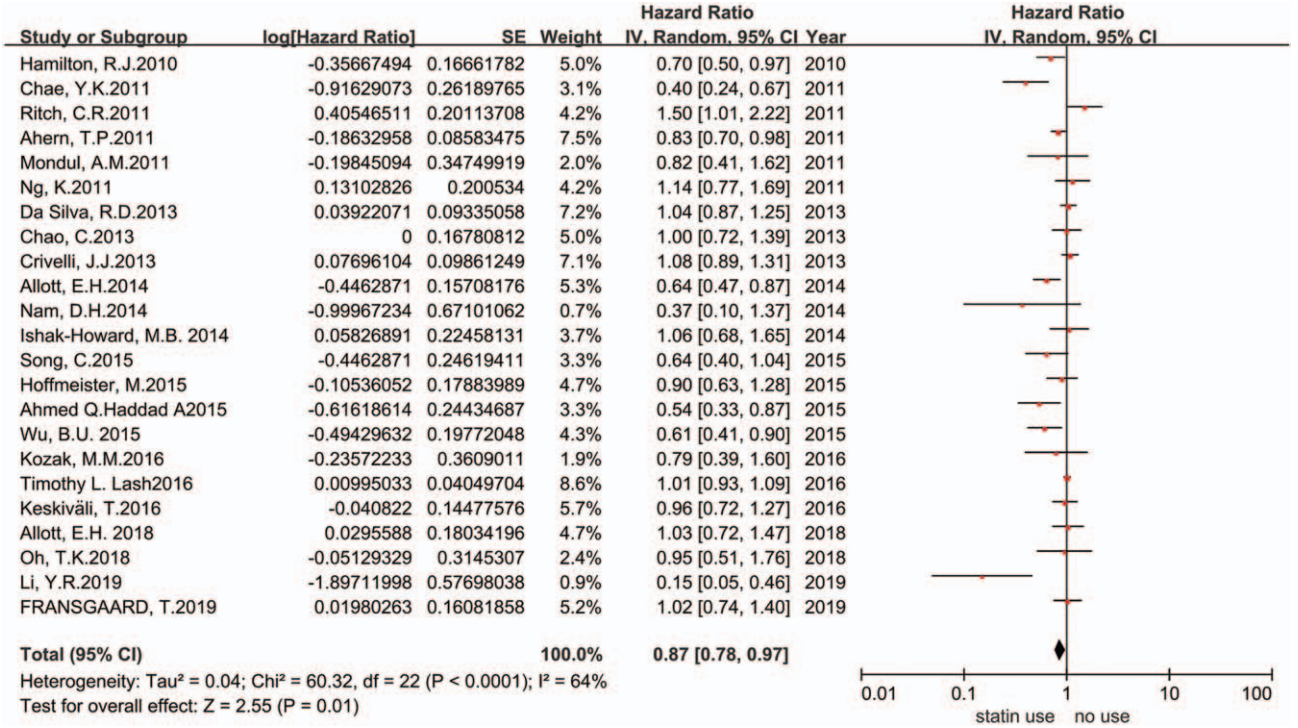

Figure 4. Forest plot of association between statin use and RFS (recurrence-free survival).

enzyme inhibitor, beta-blockers. Another analysis of 19 studies that adjusted for comorbidity (pooled HR, 0.81; 95% CI: 0.77 to 0.86). The comorbidity included cardiovascular, diabetes, respiratory, hypertension and stroke. In cancer recurrence, we performed 2 analyses including an average follow-up of more than 5 years and adjusted for combination medication. The result was 0.79 (95%CI=0.63,0.99) and 0.88 (95%CI=0.75,1.03) respectively. All subgroup and sensitivity analysis data were shown in Table 2.

4. Discussion

In our main analysis of CSM, based on 38 observational studies, we found that cancer patients taking statin have a modest reduction in cancer-cause mortality with heterogeneity across studies. Subgroup analysis enhanced the impact of statin exposure on the risk of pre-diagnosis of cancer. Sensitivity analyses suggested that the CSM result remained statistically significant when combined with estimates of studies that adjusted for using concomitant drug or comorbidity, as well as studies that

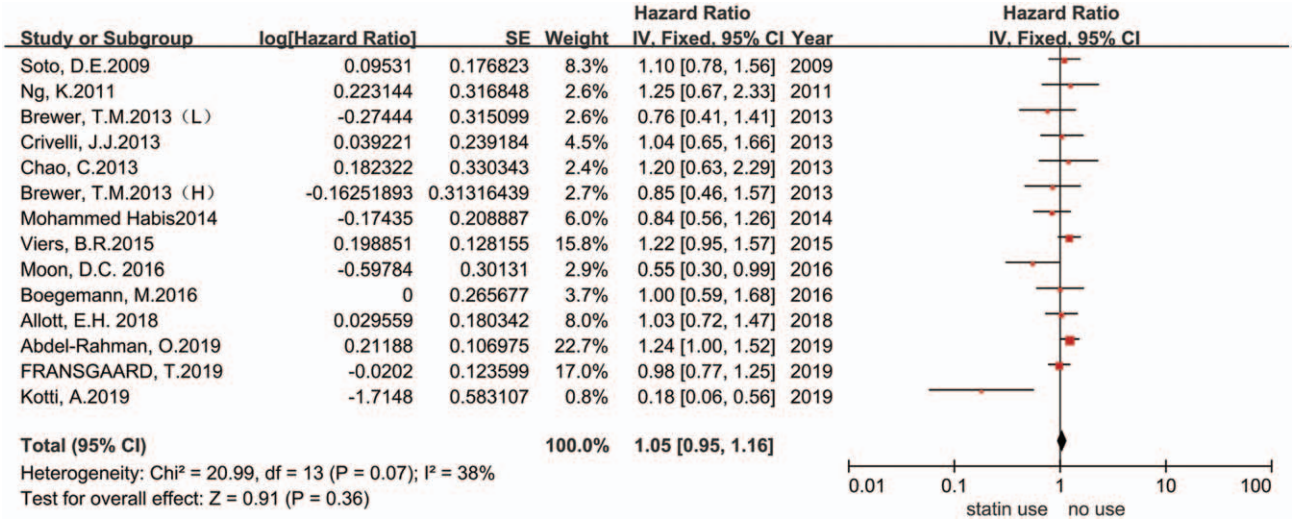

Figure 5. Forest plot of association between statin use and PFS (progression-free survival).

Table 2

Summary pooled HR (95% CI) for subgroups and sensitivity analyses of cancer-specific mortality (CSM) or recurrence-free survival (RFS) using random-effects models.

Study	Outcome	HR (random)	95%CI	Degree of heterogeneity I^2	*P*	Numbers of included studies
sensitivity analyses						
studies with median follow-up duration (>5 yr)	CSM	0.80	0.73–0.87	45	<.00001	10
studies adjusted for concomitant drug	CSM	0.82	0.77–0.87	51	<.00001	20
studies adjusted for cancer comorbidity	CSM	0.81	0.77–0.86	51	<.00001	19
studies adjusted for concomitant drug	RFS	0.88	0.75–1.03	47	.11	7
studies with median follow-up duration (>5 years)	RFS	0.79	0.63–0.99	72	.04	12
subgroup analyses						
pre-diagnostic statin use	CSM	0.81	0.75–0.88	64	<.00001	10
breast cancer	CSM	0.79	0.63–0.99	84	.04	7
colorectal cancer	CSM	0.76	0.67–0.86	57	<.0001	7
prostate cancer	CSM	0.72	0.61–0.85	92	.0001	8
prostate cancer	RFS	0.89	0.74–1.07	53	.23	9

The concomitant drug included aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme inhibitor, beta-blockers.
The comorbidity included cardiovascular, diabetes, respiratory, hypertension and stroke.
CI = confidence interval, CSM = cancer-specific mortality, RFS = recurrence-free survival.

included longer follow-up periods, the association between statin use and survival benefits became insignificant. In our analysis of cancer RFS or PFS, based on 23 and 13 observational studies separate, indicated that statins have no significant relationship with cancer recurrence or progression. Sensitivity analyses of recurrence on longer follow-up period showed little chance of reducing recurrence based on the forest plot.

Statins are commonly used to reduce cholesterol levels and are associated with a decrease in the prevalence of cardiovascular events, they lower cholesterol by inhibiting HMG-CoA reductase, the rate-limiting enzyme of the mevalonate pathway for de novo synthesis of cholesterol. And statins may have potential influence on the cancer development and progression. Some previous studies have reported the relationship between statin use and cancer risk. They studied clinical trials and literature on breast cancer, colorectal cancer, lung cancer, prostate cancer, and female reproductive organ cancer. They pointed out that trials and epidemiological studies were more feasible for cancer prognosis than event risk[79,80]. These also provided the basis for the starting point of our article. As was well known, cholesterol-synthesis pathway had great significance for cellular functions, including protein synthesis, signaling, maintaining membrane integrity, and cell-cycle progression. It was recently found that statins were involved in the onset and progression of cancer by blocking the conversion of HMG-CoA into mevalonate, to modify and activate proteins [39] and to induce tumor-specific apoptosis .[81] Statins inhibit the production of mevalonate by inhibiting HMG-CoA reductase, thereby reducing farnesyl pyrophosphate, geranyl pyrophosphate, as an intermediate of the mevalonate pathway. These intermediates regulate various cellular functions such as cell signaling pathways, cellular respiration, glycoprotein production, and cell membrane composition .[82] A study of colorectal cancer suggested that the use of statins may be associated with a cancer prognosis based on KRAS mutation status .[83] Statins favorably impede mutp53–tumor growth. And DNAJA1 could be a crucial downstream effector of statin-induced mutp53 degradation via CHIP .[84] Statins acted differently in malignant and metastatic cancer cells by perturbing various intracellular key components like iron, NO and ROS .[85] Some had developed biomarker that identifying an initial signature for statin sensitivity in human cancer cell lines and tumors,[86] they demonstrated that membrane E-cadherin was a marker of statin-resistant cells. Similar study identified vimentin as a direct molecular target that mediates simvastatin-induced cell death in 2 different cancer cell lines .[87] They found Vimentin as a potential determinant of the sensitivity of cancer cells to statin .[87,88] It is stated above that statins can affect the growth and apoptosis of cancer cells in a variety of ways.

Before our study, a recently published meta-analysis conducted by Mei Z et al involving 1,111,407 patients in 95 cohorts arrived at similar conclusions .[89] They compared the main outcome all-cause mortality in the paper. Then we primarily analyzed the CSM and recurrence free survival indicators, all the included studies were published in recent years, which could decrease variability in confounders such as diagnostic methods and treatment of cancers. Furthermore, high quality study with 7 or more NOS scores included in our study. Although we reached similar conclusions, however, the literature included in such analysis were observational studies, the above and our findings still did not demonstrate whether the use of statins is directly related to improved survival. Farooqi, M.A.M. et al systematically reviewed and meta-analyzed the effects between statins and cancer survival outcomes in randomized clinical trials. They pointed out that for patients with advanced cancer and a prognosis of less than 2 years, the addition of statins to standard anticancer treatment does not seem to improve overall survival or progression-free survival[90]. In our study, CMS results with a follow-up time of more than 5 years were HR, 0.80; 95% CI: 0.73 to 0.87, The result of PFS for more than 5 years follow-up period was 0.79 (95% CI = 0.63, 0.99). Perhaps patients with a better prognosis such as the breast cancer, prostate cancer may benefit from long-term statin treatment.

Several potential limitations deserve comment. First, significant between study heterogeneity, which may be resulted from different study designs, population sample, cancer sites and adjusted variables. Although the multivariate Cox proportional hazards model is the most commonly used method in survival analysis, the confounding covariates are different between studies. The study included a large difference in follow-up time. For example, pancreatic cancer [28,32,43] which limited by survival time did not indicate how long the period was, and the rest follow-up period ranged from 2 to 5 years and above, which may

cause 1 of the factors of greater heterogeneity. Second, potential publication bias was revealed through funnel plot, which indicated that potential missing publications was existing. We found that the use of statins seemed associated with improved CSM with significant publication bias. Limited number of studies and different cancer sites may account for the asymmetry. Although almost all included studies provided adjusted estimates considering important confounders, residual confounding may be an issue for biasing the results. Third, the included studies were different in terms of definitions of drug exposure, and most studies did not show that whether the use of statin was pre-diagnosis or post-diagnosis, Lipophilic statin and hydrophilic statin, which may lead to a part of the heterogeneity between the studies. At the same time, we also found that people who had given statins for other reasons before the diagnosis had a lower mortality rate. Statins are a relatively heterogeneous class of drugs, particularly when considering their effects unrelated to cholesterol lowering. Different doses of statins or specific statins may have different effects on cancer prognosis. We are unable to obtain such data. Fourth, the data from prostate cancer recurrence obtained from this study were biochemical recurrence. But prostate cancer biochemical recurrence may be different from other cancers. Statins may influence prostate biology through non-cholesterol-mediated, or direct, pathways too. More studies may lead to the opposite conclusion. Fifth, sensitivity analysis of CSM showed that the associations were almost consistent among these results when stratified according to median follow-up time (>5 years), concomitant drug, and cancer comorbidity. But this result did not show a significant difference in cancer recurrence. Finally, the confounding factors included in each document such as age, comorbidity, status, sex, treatment, BMI, smoking, and so on are still unpredictable.

5. Conclusions

In summary, the results of this meta-analysis suggest that the use of statins may moderately reduce cancer-specific mortality. However, caution must be exercised in interpreting these questions, as we still cannot rule out the limitations of potential methodological individual studies. And there may be biases in introducing these findings. Many of the treatments that are beneficial for non-random cohort analysis have shown no benefit when tested in randomized clinical trials. More clinical studies especially randomized controlled trials, are warranted to confirm these associations. The mechanism by which statins interact with cancer also requires further research.

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