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EDITORIAL

The relationship between statins and breast cancer prognosis varies by statin type and exposure time: a meta-analysis

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Abstract
Purpose Breast cancer is the most common cancer in females and the leading cause of death worldwide. The effects of statins on breast cancer prognosis have long been controversial; thus, it is important to investigate the relationship between statin type, exposure time, and breast cancer prognosis. This study sought to explore the effect of statins, as well as the different effects of statin solubility and variable follow-up times, on breast cancer prognosis.
Methods We searched the MEDLINE (via PubMed), EMBASE (via OvidSP), Cochrane Library, and ISI Web of Knowledge databases using combinations of the terms "breast neoplasms[MeSH]," "statins" or "lipid-lowering drug," "prognosis" or "survival," or "mortality" or "outcome" with no limit on the publication date. We searched the databases between inception and October 15, 2016. Reference lists of the included studies and relevant reviews were also manually screened. The initial search identified 71 publications, and 7 of these studies, which included a total of 197,048 women, met the selection criteria. Two authors independently screened each study for inclusion and extracted the data. The data were analyzed using Stata/SE 11.0.
Results Overall statin use was associated with lower cancer-specific mortality and all-cause mortality, although the benefit appeared to be constrained by statin type and follow-up time. Lipophilic statins were associated with decreased breast cancer-specific and all-cause mortality; however, hydrophilic statins were weakly protective against only all-cause mortality and not breast cancer-specific mortality. Of note, one group with more than 4 years of follow-up did not show a significant correlation between statin use and cancer-specific mortality or all-cause mortality, whereas groups with less than 4 years of follow-up still showed the protective effect of statins against cancer-specific mortality and all-cause mortality.
Conclusions Although statins can reduce breast cancer patient mortality, the benefit appears to be constrained by statin type and follow-up time. Lipophilic statins showed a strong protective function in breast cancer patients, whereas hydrophilic statins only slightly improved all-cause mortality. Finally, the protective effect of statins could only be observed in groups with less than 4 years of follow-up. These findings are meaningful in clinical practice, although some conclusions contradict conventional wisdom and will thus require further exploration.

Keywords Statin · Breast cancer · Lipophilic · Hydrophilic · Follow-up time · Mortality

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Introduction

Inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA), known as statins, are a group of drugs that are used worldwide for their confirmed curative

effect on lipid disorders, in particular hypercholesterolemia. The efficacy of statins in preventing the development of cardiovascular diseases and improving the outcome of cardiovascular disease has been well documented [1].

Different statin types have different impacts on breast cancer, and some research indicates that statins might play an important role in cancer due to their protective effect on the development of various types of cancers [1].

Breast cancer is the most common cancer in females and is the leading cause of death worldwide [2]. However, the relationship between statins and breast cancer incidence and prognosis remains contradictory and unclear.

Statins can be divided into two types based on their solubility: hydrophobic statins (pravastatin, rosuvastatin) and lipophilic statin (simvastatin, lovastatin, fluvastatin, atorvastatin). An increasing number of articles have found that the solubility of statins may produce different results. A meta-analysis conducted by Signe Borgquist showed no association between overall statin use and the risk of invasive breast cancer, although hydrophobic statins were associated with a significantly reduced breast cancer incidence. The same result was confirmed by Gaia Pocobelli et al. [3, 4]. However, Pinkal Desai et al. and Thunyarat Anothaisintawee found a lower hazard ratio of breast cancer for lipophilic statins than hydrophobic statins [5, 6].

According to the literature, the study with the longest follow-up period ($\geq$10 years) showed an approximately 20% reduced risk of breast cancer [7], whereas shorter follow-up studies did not obtain similar results. Thus, it seems that the type of statin and the duration of statin use can influence the preventive effect on breast cancer.

All of the above findings focused on statins and breast cancer incidence. However, few studies have investigated statins in relation to the prognosis of breast cancer. Although two meta-analyses have been conducted on this topic, each one had an obvious limitation (an insufficient number of studies included and no unified end point) [8, 9]. Other studies included inconsistent measures, such as risk, recurrence, and mortality, indicating that the results might be biased. Moreover, no meta-analysis has focused on the relationship between different statin exposure times and different prognoses of breast cancer. Here, we used mortality as a unified end point to explore the different relationships between statin types, exposure times, and breast cancer prognosis.

Materials and methods

Search strategy

The present meta-analysis was performed and reported according to the guidelines for diagnostic studies. The MEDLINE (via PubMed), EMBASE (via OvidSP), Cochrane Library, and ISI Web of Knowledge databases were searched for potentially relevant studies without restriction to regions or publication types. The search strategy included a combination of the following key words and medical subheadings: "breast neoplasms[MeSH]," "statins" or "lipid-lowering drug," "prognosis" or "survival," or "mortality" or "outcome." We searched the databases between inception and October 15, 2016. Reference lists of included studies and relevant reviews were also manually screened.

Inclusion and exclusion criteria

Inclusion criteria

Records retrieved from databases and reference lists were first screened by title and abstract, and then full-text articles were further reviewed for eligibility. Eligible studies were selected according to the following inclusion criteria: (a) patients with breast cancer diagnosed histopathologically or cytologically, regardless of tumor stage, duration of statin use (before or after the diagnosis), statin type, or ethnicity; (b) sufficient information provided for hazard ratio (HR), 95% confidence interval (CI), and *P*-values for patient mortality; and (c) accurate follow-up times.

Exclusion criteria

The following exclusion criteria were applied: (a) the research aimed to reveal the relationship between statin and breast cancer risk or incidence; and (b) duplicate reports from the same center.

All records were independently reviewed by the authors, and a consensus was reached on each eligible study.

Data extraction

Two authors (BL and ZB) independently searched the eligible papers, and the extracted data included HRs and 95% CIs for mortality. For studies with insufficient information, we attempted to contact the primary authors or use the data from the paper to calculate the data that we needed using Stata/SE 11.0 (StataCorp LP). Two authors (BL and ZB) extracted these data independently, and discrepancies between the two authors were resolved by discussion or consensus with our mentors.

Quality assessment

The methodological quality of retrospective studies was assessed with the modified Newcastle–Ottawa Scale (NOS). This scale is based on four broad categories relating

to the selection of the study sample (four points), the comparability of the sample groups (two points), and the ascertainment of either the exposure for case–control (three points) and cross-sectional studies (two points) or the outcome for cohort studies (three points). Achieving seven or more points was regarded as high methodological quality. The methodological quality of eligible studies was evaluated by two investigators.

Statistical analysis

The data analyses were performed using Stata/SE 11.0. We aggregated the data of HRs and 95% CIs and used the log function to perform a meta-analysis (loghr and SEloghr). From the data we collected, we found the values of HRs to be mostly above or below 1; therefore, we used the exponent to make our result a positive number. First, we calculated the overall statin use and breast cancer prognosis (mortality). Then, according to the type of statin or follow-up time, we divided each into two groups to compare mortality rates. A χ^2-based Q statistic and inconsistency index (I^2) statistic were used to examine heterogeneity. P-values <0.1 and I^2values $>50\%$ indicated significant heterogeneity. A random effects model was used if the test for heterogeneity was significant; otherwise, a fixed-effects model was used. If we observed significant heterogeneity, then we performed sensitivity analyses by deleting each study individually to evaluate the quality and consistency of the results, and we performed subgroup analyses for follow-up time and pathological classification. Publication bias was evaluated using funnel plots, Begg's tests, and Egger's tests. Probable significant publication bias was considered for a P-value <0.05.

Results

Study characteristics

A total of 69 articles were identified initially by keyword searching. Seven studies were finally included in our meta-analysis. The included studies comprised 197,048 women who were identified as breast cancer patients. Six studies included all stages of breast cancer patients, and one study recruited breast cancer patients with stage II/III disease. One study only provided HRs and CIs for breast cancer-specific mortality, two studies only provided all-cause mortality, and the remaining four studies provided both cancer-specific and all-cause mortality. In five studies, different HR values and CIs were given according to statin solubility. Four studies included more than 4 years of follow-up time, while the remaining three studies did not. The main characteristics of the seven included studies are listed in Table 1. The included studies were published between 2011 and 2016. A flow diagram is shown below.

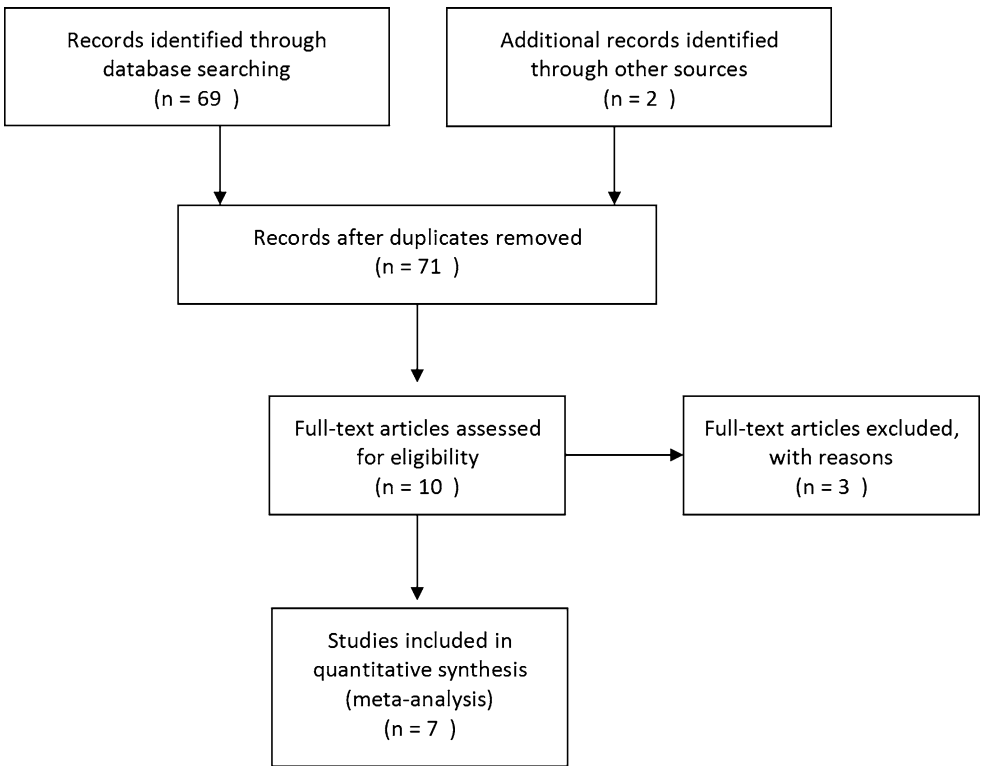


Table 1 Characteristics of the eligible studies included in the meta-analysis

Author	Year	Country	Sample size	Sample qualification	Stage	Study design	Outcome			Median follow-up time (in years)	NOS
							Varied by death cause	Varied by statin type	Varied by statin use time (before and after diagnosis)		
Úna C. Mc Menamin [10]	2016	UK	15,140	Invasive breast cancer diagnosed in Scottish Cancer Registry	I–IV	Retrospective cohort	Yes	Yes	Yes	4	8
Pinkal Desai [5]	2015	USA	128,675	Post-menopausal women aged 50–79 years	I–IV	Retrospective cohort	Yes	Yes	Yes	11.5	8
CR Cardwell [11]	2015	UK	17,880	Diagnosed in English cancer registries	I–IV	Retrospective cohort	Yes	Yes	No	5.7	8
Teemu J. Murtola [12]	2014	Finland	31,236	Diagnosed in Finland cancer registry	I–IV	Retrospective cohort	Yes	Yes	Yes	3.25	8
Stefan Nickels [13]	2013	Germany	3189	German MARIEplus study	I–IV	Prospective cohort	Yes	No	No	5.3	9
Young Kwang Chae [14]	2011	USA	703	Diagnosed in Albert Einstein Medical Center	II/III	Retrospective cohort	No	No	No	4.6	8
A. C. Ceacareanu [15]	2011	USA	225	Diabetes mellitus patients with breast cancer diagnosed in Roswell Park Cancer Institute	I–IV	Retrospective cohort	No	No	No	2.5	8

Overall statin use and mortality

Seven articles reported multivariable HRs and their respective 95% CIs, while some studies used cancer-specific mortality and others used all-cause mortality. Thus, we also separated these studies into two categories according to the causes of death (Fig. 1a, b). Eventually, pooled analyses of the seven studies reported multivariable HRs, showing that there was significant inter-study heterogeneity ($I^2 = 85.6$ and 87.4%). Thus, we used a random effects model. From the results, we found that the use of statins was associated with reduced breast cancer mortality, including both breast cancer-specific and all-cause mortality (cancer-specific mortality: HR 0.73, 95% CI 0.59–0.92, $P = 0.000$; all-cause mortality: HR 0.72, 95% CI 0.58–0.89, $P = 0.000$).

Median follow-up time and mortality (subgroup analysis)

We sorted the seven articles into two subgroups by follow-up time. When we established a 4-year follow-up period as the cutoff value, the studies could be divided almost equally. The results suggested that more than 4 years of follow-up did not show a significant association between statin use and cancer-specific mortality (HR 0.84, 95% CI 0.71–1.00, $P = 0.616$) or all-cause mortality (HR 0.95, 95% CI 0.75–1.19, $P = 0.181$); the corresponding I^2 values were 0.0 and 41.5%, respectively, which were significantly reduced. In contrast, less than 4 years of follow-up still showed a protective effect of statins against cancer-specific mortality (HR 0.62, 95% CI 0.44–0.87, $P = 0.000$) as well as all-cause mortality (HR 0.61, 95% CI 0.45–0.80, $P = 0.000$). However, the I^2 value was higher, which influences the reliability. The longer the follow-up time, the longer was the duration of statin use. Thus, if we consider follow-up time as statin use time, these differences become much more meaningful (Fig. 2a, b).

Different types of statins and mortality

Statins can be divided into two types based on their solubility: hydrophobic statins (pravastatin, rosuvastatin) and lipophilic statin (simvastatin, lovastatin, fluvastatin, atorvastatin). The current research results suggest that different types of statins work differently in terms of breast cancer mortality prognosis. Four studies reported the HR and CI results of different statins on breast cancer mortality. From the final meta-analysis result, we found significant protective effects of lipophilic statin use against both cancer-specific mortality and all-cause mortality (HR 0.57, 95% CI 0.46–0.70, $P = 0.000$ and HR 0.57, 95% CI 0.48–0.69, $P = 0.000$) (Fig. 3a, b).

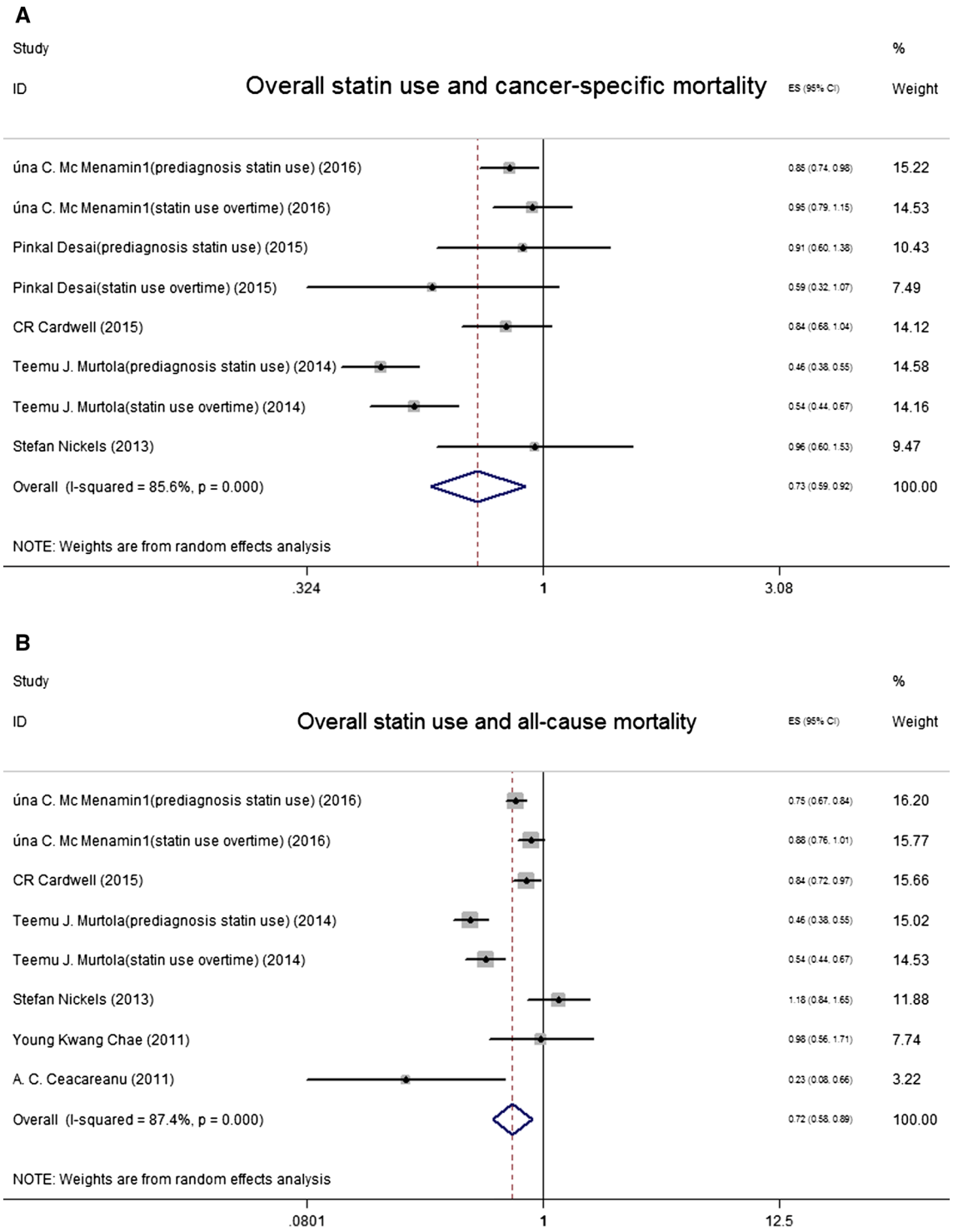
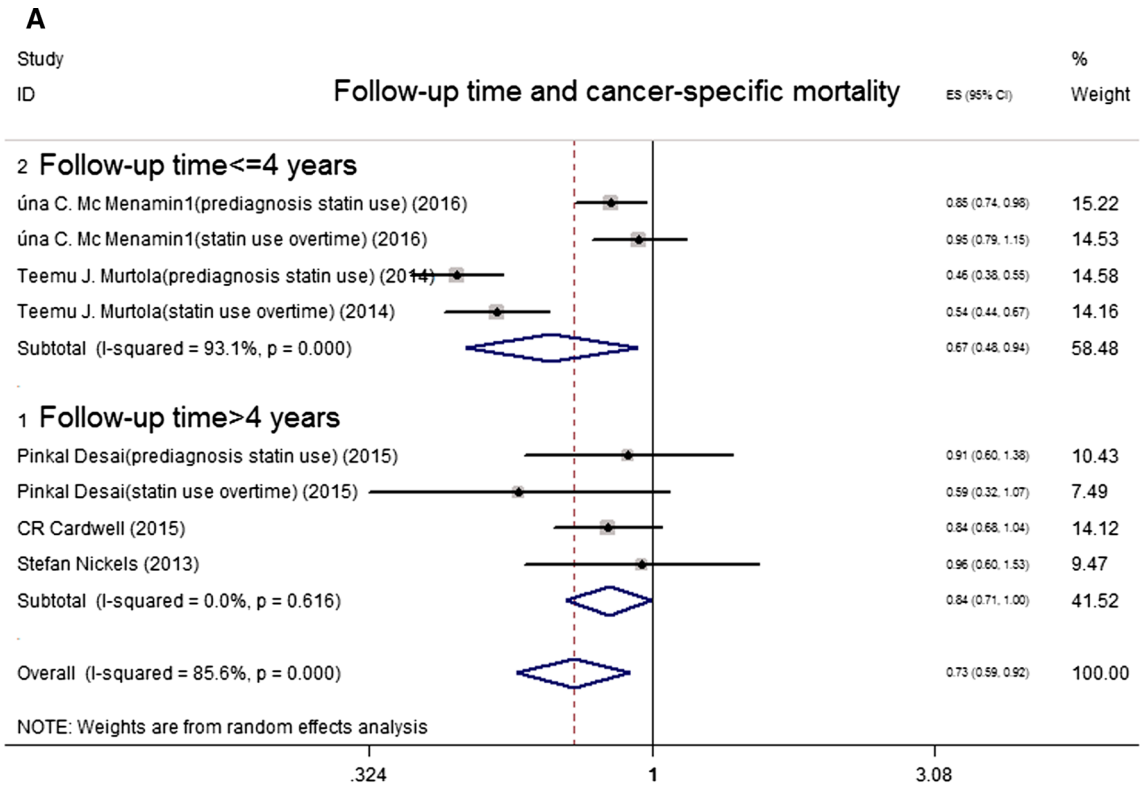


Fig. 1 **a** Overall statin use and breast cancer-specific mortality (pre-diagnosis: statin use before diagnosis; overtime: statin use over time). **b** Overall statin use and all-cause mortality

However, hydrophilic statins were only protective against all-cause mortality (HR 0.79, 95% CI 0.65–0.97, $P = 0.132$) and not breast cancer-specific mortality (HR 0.94, 95% CI 0.76–1.17, $P = 0.174$) (Fig. 3c, d).

Publication bias

Publication bias was examined using funnel plots, Begg's test and Egger's regression test. We performed each meta-



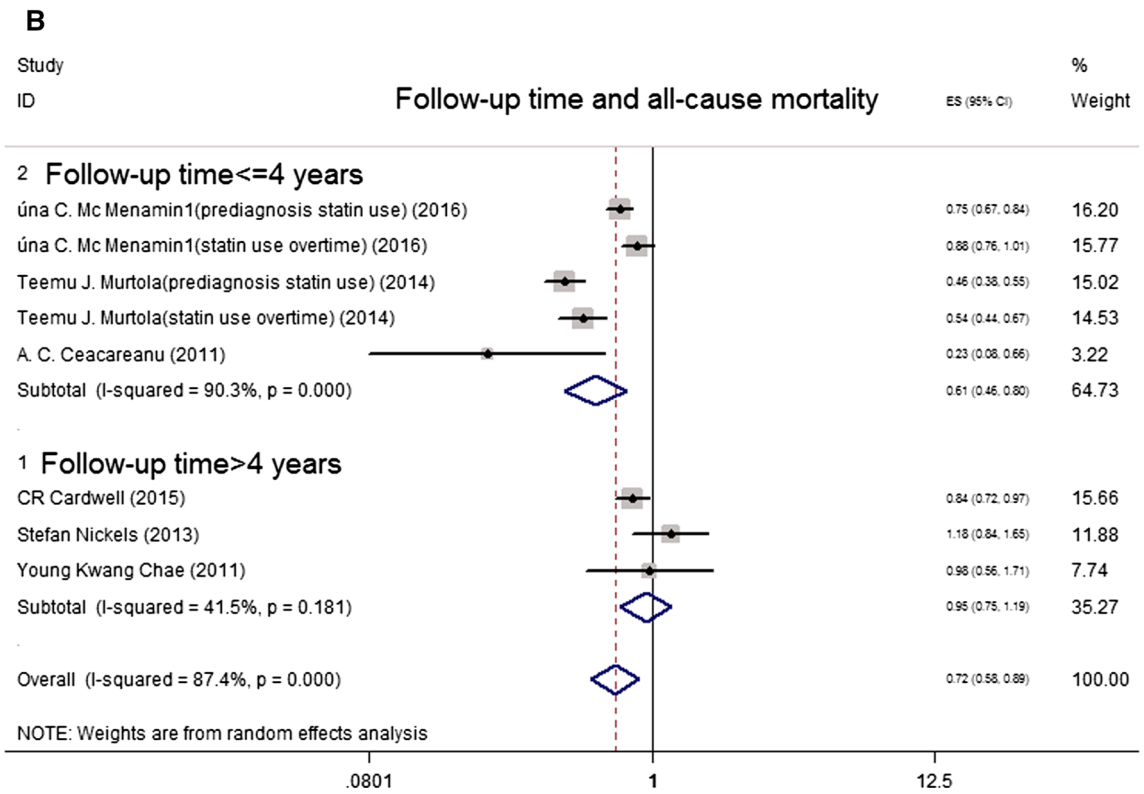
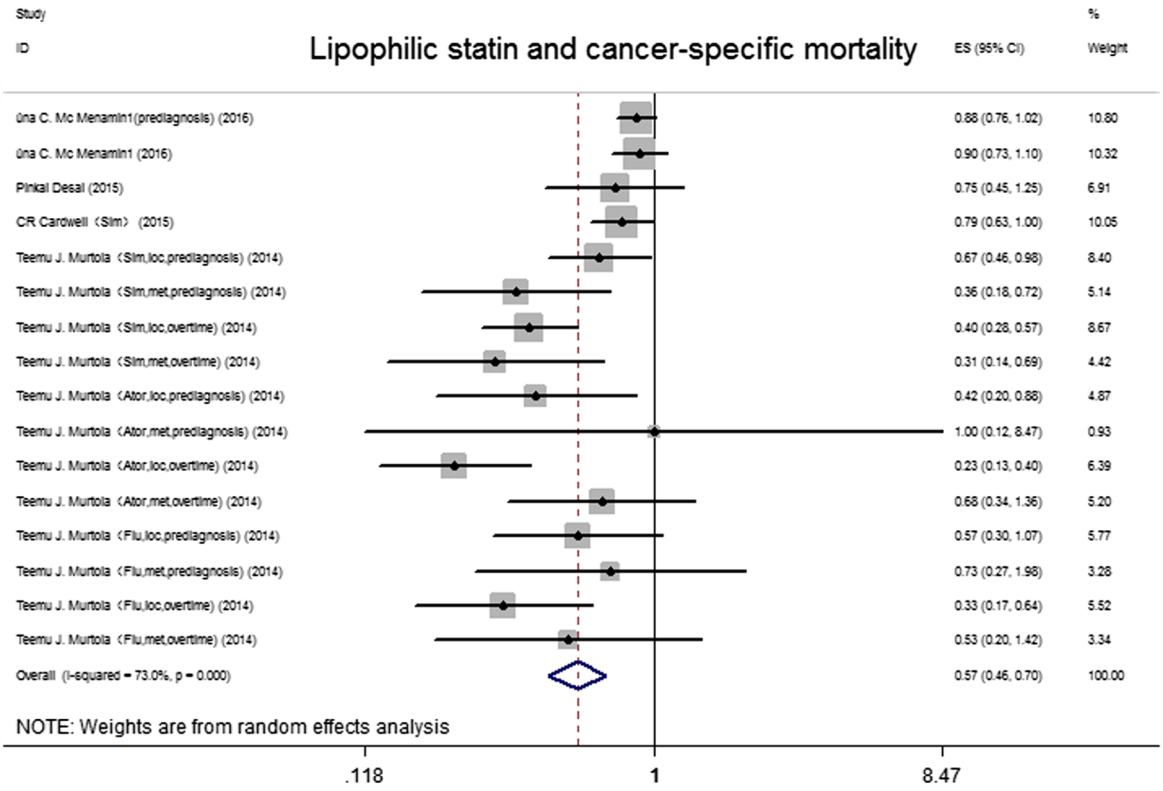
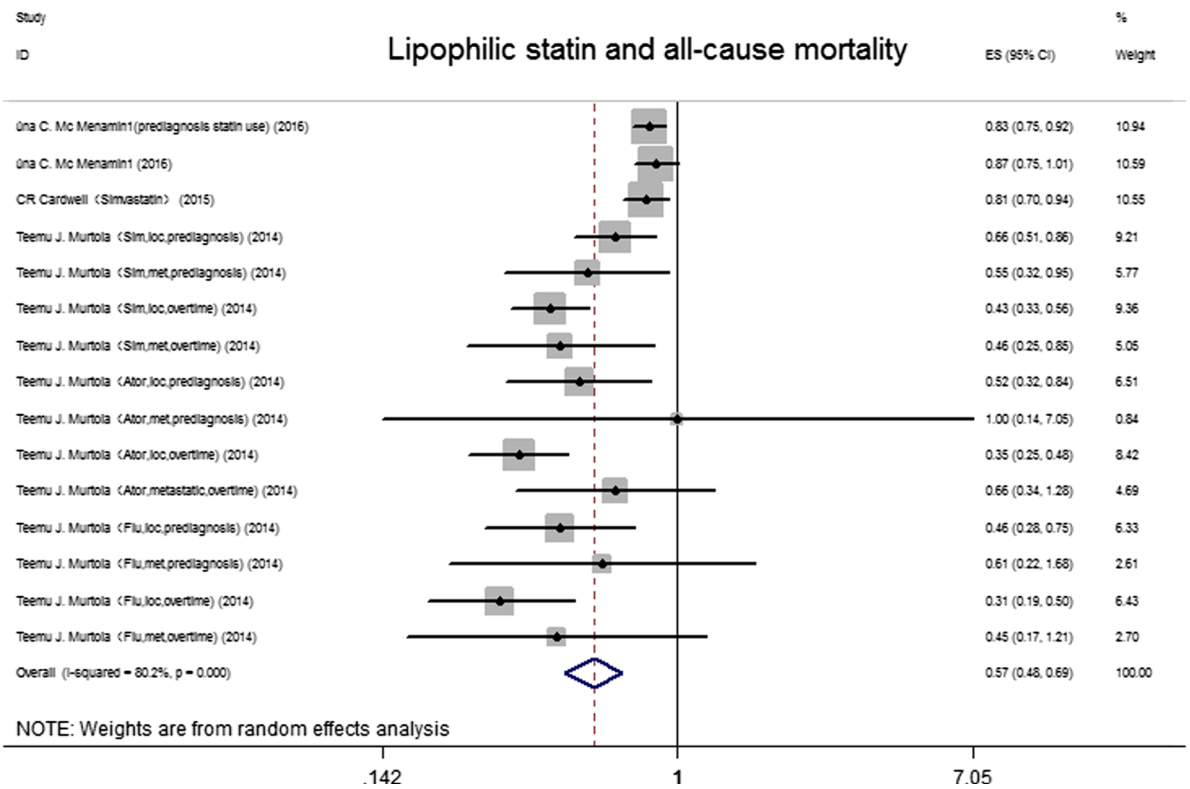


Fig. 2 **a** Overall statin use and cancer-specific mortality subgroup analysis varied by follow-up time. **b** Overall statin use and all-cause mortality subgroup analysis varied by follow-up time

A


Study
ID
Lipophilic statin and cancer-specific mortality
ES (95% CI)
%
Weight
úna C. Mc Menamin1(prediagnosis) (2016) 0.88 (0.76, 1.02) 10.80
úna C. Mc Menamin1 (2016) 0.90 (0.73, 1.10) 10.32
Pinkal Desai (2015) 0.75 (0.45, 1.25) 6.91
CR Cardwell 〈Sim〉 (2015) 0.79 (0.63, 1.00) 10.05
Teemu J. Murtola 〈Sim,loc,prediagnosis) (2014) 0.67 (0.46, 0.98) 8.40
Teemu J. Murtola 〈Sim,met,prediagnosis) (2014) 0.36 (0.18, 0.72) 5.14
Teemu J. Murtola 〈Sim,loc,overtime) (2014) 0.40 (0.28, 0.57) 8.67
Teemu J. Murtola 〈Sim,met,overtime) (2014) 0.31 (0.14, 0.69) 4.42
Teemu J. Murtola 〈Ator,loc,prediagnosis) (2014) 0.42 (0.20, 0.88) 4.87
Teemu J. Murtola 〈Ator,met,prediagnosis) (2014) 1.00 (0.12, 8.47) 0.93
Teemu J. Murtola 〈Ator,loc,overtime) (2014) 0.23 (0.13, 0.40) 6.39
Teemu J. Murtola 〈Ator,met,overtime) (2014) 0.68 (0.34, 1.36) 5.20
Teemu J. Murtola 〈Flu,loc,prediagnosis) (2014) 0.57 (0.30, 1.07) 5.77
Teemu J. Murtola 〈Flu,met,prediagnosis) (2014) 0.73 (0.27, 1.98) 3.28
Teemu J. Murtola 〈Flu,loc,overtime) (2014) 0.33 (0.17, 0.64) 5.52
Teemu J. Murtola 〈Flu,met,overtime) (2014) 0.53 (0.20, 1.42) 3.34
Overall (I-squared = 73.0%, p = 0.000) 0.57 (0.46, 0.70) 100.00
NOTE: Weights are from random effects analysis
.118
1
8.47

B


Study
ID
Lipophilic statin and all-cause mortality
ES (95% CI)
%
Weight
úna C. Mc Menamin1(prediagnosis statin use) (2016) 0.83 (0.75, 0.92) 10.94
úna C. Mc Menamin1 (2016) 0.87 (0.75, 1.01) 10.59
CR Cardwell 〈Simvastatin〉 (2015) 0.81 (0.70, 0.94) 10.55
Teemu J. Murtola 〈Sim,loc,prediagnosis) (2014) 0.66 (0.51, 0.86) 9.21
Teemu J. Murtola 〈Sim,met,prediagnosis) (2014) 0.55 (0.32, 0.95) 5.77
Teemu J. Murtola 〈Sim,loc,overtime) (2014) 0.43 (0.33, 0.56) 9.36
Teemu J. Murtola 〈Sim,met,overtime) (2014) 0.46 (0.25, 0.85) 5.05
Teemu J. Murtola 〈Ator,loc,prediagnosis) (2014) 0.52 (0.32, 0.84) 6.51
Teemu J. Murtola 〈Ator,met,prediagnosis) (2014) 1.00 (0.14, 7.05) 0.84
Teemu J. Murtola 〈Ator,loc,overtime) (2014) 0.35 (0.25, 0.48) 8.42
Teemu J. Murtola 〈Ator,metastatic,overtime) (2014) 0.66 (0.34, 1.28) 4.69
Teemu J. Murtola 〈Flu,loc,prediagnosis) (2014) 0.46 (0.28, 0.75) 6.33
Teemu J. Murtola 〈Flu,met,prediagnosis) (2014) 0.61 (0.22, 1.68) 2.61
Teemu J. Murtola 〈Flu,loc,overtime) (2014) 0.31 (0.19, 0.50) 6.43
Teemu J. Murtola 〈Flu,met,overtime) (2014) 0.45 (0.17, 1.21) 2.70
Overall (I-squared = 80.2%, p = 0.000) 0.57 (0.48, 0.69) 100.00
NOTE: Weights are from random effects analysis
.142
1
7.05

◀**Fig. 3** **a** Lipophilic statin use and cancer-specific mortality (prediagnosis: statin use before diagnosis; overtime: statin use over time; *sim* simvastatin; *asor* atorvastatin; *flu* fluvastatin; *loc* localized; *met* metastatic). **b** Lipophilic statin use and all-cause mortality. **c** Hydrophilic statin use and cancer-specific mortality. **d** Hydrophilic statin use and all-cause mortality

analysis once, respectively; thus, six independent examinations were conducted in this study (Table 2). From Begg's test, no evidence of publication bias was found. However, from Egger's test, two of six publications showed some evidence of bias with the consequence of credibility loss.

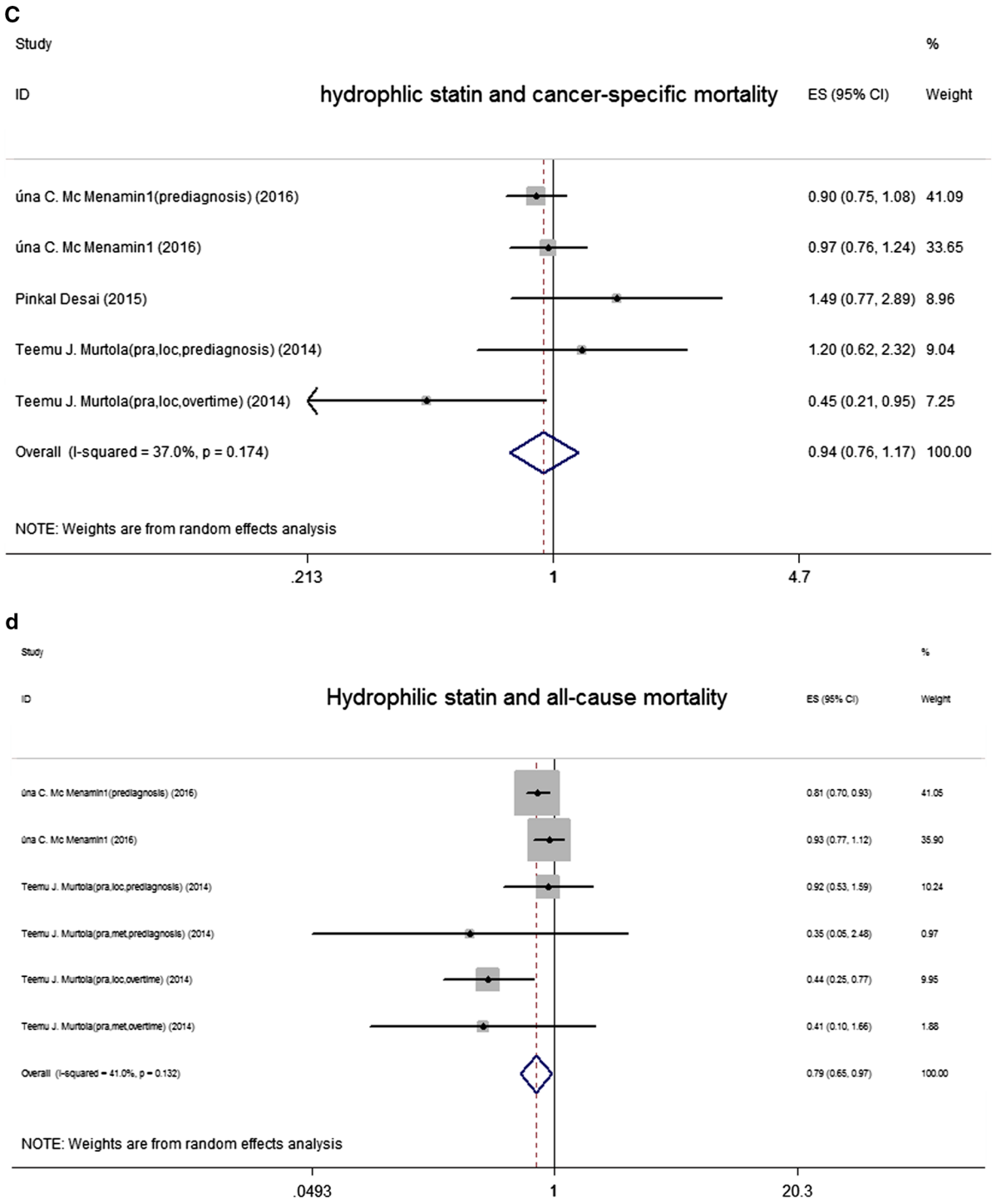


Fig. 3 continued

Table 2 Publication bias

Meta-analysis	Begg's test		Egger's test	
	Z-value	*P*-value	*T*-value	*P*-value
Overall statin and cancer-specific mortality	0.37	0.711	0.00	0.998
Overall statin and all-cause mortality	0.12	0.902	−0.40	0.702
Lipophilic statin and cancer-specific mortality	0.77	0.444	−3.28	0.005
Lipophilic statin and all-cause mortality	0.00	1.000	−2.89	0.013
Hydrophilic statin and cancer-specific mortality	0.24	0.806	0.11	0.922
Hydrophilic statin and all-cause mortality	0.75	0.452	−1.52	0.203

Quality assessment

All the articles were of high quality. One study achieved a score of nine, and the remaining six studies achieved scores of eight.

Discussion

With the improvement of living standards, people's diets are increasingly abundant, and dietary fat consumption is elevated. Many papers have shown that increased serum lipid levels lead to higher risks and a worse breast cancer prognosis [16–18]. HMG-CoA inhibitors, which are also known as statins, are a therapeutic class of drugs that regulate plasma lipid levels to reduce the risk of cardiovascular and cerebrovascular incidence over a long time period. Recently, more and more researchers have demonstrated the relationship between statins and cancer. Two previous studies performed meta-analyses but suffered obvious limitations in terms of an insufficient number of included studies and the lack of unified end points [8, 9]. Some articles have previously shown that different statin types may have different effects on breast cancer incidence [3–5] and prognosis [5, 10–12, 19]. Thus, we preformed the current meta-analysis using mortality as the unified end point; moreover, we sought to explore the different influences of statin types and different follow-up times on the prognosis of breast cancer.

In this report, we demonstrate that overall statin use is associated with decreased cancer-specific mortality and all-cause mortality. This finding is consistent with virtually all previously reported data (cancer-specific mortality: HR 0.73, 95% CI 0.59–0.92, $P = 0.000$; all-cause mortality: HR 0.72, 95% CI 0.58–0.89, $P = 0.000$). In addition, many articles have confirmed that the use of statins can reduce breast cancer incidence and the risk of recurrence [13, 14], thus indicating the wide-ranging protective effects of statins in patients with breast cancer. However, the mechanism for how statins improve the prognosis of patients with cancer differs from that in the cardiovascular field. Indeed, the role of statins is far greater than a simple lipid-lowering effect or the inhibition of tumor proliferation. For instance, studies have demonstrated the involvement of statins in signaling pathways such as Ras/MAPK, JAK/SAPK, PI3 k/AKT, and NF-κB due to the suppression of the mevalonate pathway [20–24]. Through a meta-analysis of six microarray datasets, the mevalonate pathway has been confirmed to correlate with a poor prognosis in primary breast cancer [25]. In addition, the induction of cell cycle (G1/S) arrest in tumor cells, the activation of cellular autophagy, and the inhibition of angiogenesis have also been confirmed in cell culture experiments [22, 24]. Statin inhibition of embryonic stem cells and cancer stem cells through the suppression of a stemness pathway has also been reported [24].

Further exploration of this topic may provide better insight into the relationship between statins and breast cancer prognoses, particularly the differences between different statin types and follow-up times. We found that lipophilic statins showed significant protective effects against cancer-specific and all-cause mortality. However, hydrophilic statins were protective against only all-cause mortality and not breast cancer-specific mortality.

In fact, the class-specific anti-proliferative effects of statins have been confirmed in many in vivo or in vitro experiments. At least two cell culture experiments confirmed that lipophilic statins could inhibit breast cancer cell proliferation, while this result was not observed for hydrophilic statins [23, 26]. Moreover, lipophilic statins can penetrate the cell plasma membrane more easily than hydrophilic statins, and the cellular penetration of lipophilic statins may be associated with their inhibition of cell growth. This hypothesis is supported by the finding that lipophilic statins significantly inhibited the growth of mouse mammary carcinoma cells while hydrophilic statins did not [27]. One pharmacokinetic study confirmed that the hepatocyte selectivity of hydrophilic statins was greater than that of lipophilic statins for unknown reasons [28], which indicates that reduced statin uptake by non-hepatic tissues could limit the protective function of statins. These observations are consistent with our results. As is well known, the cytotoxic activity of immunological effects plays an important role in the killing of cancer cells, and

lipophilic statins have been reported to stimulate monocytes to release cytokines (MCP-1, IL-8, TNF-a, and IL-1b) and induce leukocyte influx into the lesion through an as-yet-unknown mechanism; in contrast, hydrophilic pravastatin did not induce these heightened inflammatory responses [29].

As for follow-up time, one group with more than 4 years of follow-up did not show a significant association between statin use and cancer-specific mortality or all-cause mortality. Although this finding appears to contradict conventional wisdom, in the year 2008, Pocobelli found that fluvastatin is associated with a reduced risk of breast cancer only during the first 5 years [4], and we can provide some possible explanations for this finding. (1) On average, the deceased patients only accounted for a minority of the study population. In our study, the longest median follow-up time was 11.5 years in Pinkal Desai's study, which included 128,675 patients, although only 401 patients died from confirmed breast cancer [5]. The insufficient percentage of patients reaching this end point may dramatically affect the reliability of these results. (2) With the extension of follow-up time, the proportion of attrition and exclusions from the analysis will also increase, and few studies reported or analyzed patient loss to follow-up or attrition bias. (3) The mechanisms for the protective effect of statins against breast cancer likely involve pathways in addition to the blocking of HMG-CoA reductase and cannot be fully explained by a lipid-lowering effect [26, 27]. As mentioned above, the mechanism of action of statins is complicated, and the interactions between different pathways remain unclear [23] and inconsistent. For example, following statin treatment, p-MEK1/2 and NF-κB levels vary differently in the first 4 and 48 h, accompanied by different growth rates of tumor cells [21]. Although we did not observe a long-term trend, we also do not clearly understand what changes occur in the cell regulatory system after 4 years of statin intake in the human body, and we cannot rule out that statin use no longer benefits breast cancer progression.

These results, while compelling, are accompanied by limitations and raise several questions that future studies in this area should address. First, these data are mostly derived from retrospective cohort studies that have various forms of bias due to the design of such studies. Different recruitment requirements, different definitions of satin use, and different statin use durations and dosages all inevitably reduce the credibility of the analysis. In addition, some information on statin types in the reviewed articles was not complete, and some types of statin users were limited in some specific research groups, which may have led to wider confidence intervals and lower reliability. In addition, publication bias was found in two meta-analyses using Egger's test (the relationship between lipophilic statins and cancer-specific or all-cause mortality).

Because of these controversial results regarding the relationship between statins and breast cancer prognosis, which led to rather high heterogeneity in our meta-analysis, it is difficult to assign a truly advantageous benefit for this population. Thus, future studies should take ethnicity, sex, age, molecular subtype of breast cancer, cardiovascular disease status, and other factors into account to provide a more detailed recommendation for statin use in breast cancer patients.

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Compliance with ethical standards

Conflict of interest All authors declare no conflicts of interest.

Research involving human and animal rights Our study was not funded and does not contain any studies with human participants performed by any of the authors.

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